• Recombinant DNA Technology in Eukaryotes

The techniques for gene manipulation and cloning were first developed in bacteria but are now applied routinely in a variety of model eukaryotes. As stated in Chapter 2, the genomes of eukaryotes are larger and more complex than those of bacteria, so modifications of the techniques are needed to handle the larger amounts of DNA and the array of different cells and life cycles of eukaryotes. Although eukaryotic genes are cloned and sequenced in bacterial hosts, it is often desirable to introduce such genes back into the original eukaryotic host or into another eukaryote—in other words, to make a transgenic eukaryote.

Transgenic Eukaryotes

DNA is introduced into a eukaryotic cell by a variety of techniques, including transformation, injection, viral infection, or bombardment with DNA-coated tungsten particles (Figure 11-9 on the following page). As we learned in Chapter 10, when exogenously added DNA that is originally from that organism inserts into the genome, it can either replace the resident gene or insert ectopically. If the DNA is a transgene from another species, it inserts ectopically. (Vectors that replicate autonomously in eukaryotic cells are rare, so in most cases chromosomal integration is the route followed.)

The possibility of transgenic modification of eukaryotes such as plants and animals (including humans) opens up many new approaches to research because genotypes can be genetically engineered to make them suitable for some specific experiment. (An example in basic research is in the use of reporter genes. Sometimes it is difficult to detect the activity of a particular gene in the tissue where it normally functions. This problem can be circumvented by splicing the promoter of the gene in question to the coding region of a gene, known as a reporter gene, whose product *is* easily detectable. Wherever and whenever the gene in question is active, the reporter gene will announce that activity in the appropriate tissue. Examples will be given later in the chapter.)

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Furthermore, because plants, animals, and fungi form the basis for a large part of the economy, transgenic "designer" genotypes are finding extensive use in applied research. A particularly exciting application of transgenesis is in human gene therapy, the introduction of a normally functional transgene that can replace or compensate for a resident malfunctioning allele.

Recombinant DNA technology in the treatment of diabetes: insulin analogs

After more than half a century of treating diabetics with animal insulins, recombinant DNA technologies and advanced protein chemistry made human insulin preparations available in the early 1980s. As the next step, over the last decade, insulin analogs were constructed by changing the structure of the native protein with the goal of improving the therapeutic properties of it, because the pharmacokinetic characteristics of rapid-, intermediate-, and long-acting preparations of human insulin make it almost impossible to achieve sustained normoglycemia. The first clinically available insulin analog, lispro, confirmed the hopes by showing that improved glycemic control can be achieved without an increase in hypoglycemic events. Two new insulin analogs, insulin glargine and insulin aspart, have recently been approved for clinical use in the United States, and several other analogs are being intensively tested. Thus, it appears that a rapid acceleration of basic and clinical research in this arena will be seen, which will have direct significance to both patients and their physicians. The introduction of new short-acting analogs and the development of the first truly long-acting analogs and the development of analogs with increased stability, less variability, and perhaps selective action, will help to