factor VIII, and factor X. The large-scale production of tissue plasminogen activator is an important commercial process.

12.4.6. Insecticides

Animal cell cultures have been used to produce some insect viruses that are highly specific and safe to the environment. Several of the baculoviruses have federal approval for use as insecticides. Genetically engineered variants with greater virulence can now be produced. The commercial production of such viruses from tissue culture has not yet been accomplished.

12.4.7. Whole Cells and Tissue Culture

The production of differentiated cells for medical use is under early development. Artificial skin for burn patients is one example. Artificial organs and semisynthetic bone and dental structures are potentially feasible.

12.5. SUMMARY

Animal cells are well suited for the production of proteins requiring extensive and accurate posttranslational processing, organized tissues (artificial skin), certain vaccines, and viruses that can be used as pesticides.

Animal cells are more complex and fragile than bacterial, fungal, or yeast cultures. These characteristics require the development of unique strategies for cultivation.

Critical distinctions are *primary* cell lines (established directly from tissue) and *secondary* cell lines, which are established from primary cell lines. Normal cell lines are *mortal*; they can divide only a finite number of times. Other cell lines are *transformed* or *immortal* and divide indefinitely. Many cell lines will grow only when attached to a surface and are thus *anchorage dependent*. Some cells, particularly transformed cell lines, can grow in suspension. One particularly important type of suspension cell is the *hybridoma*. This cell is a hybrid of a mortal antibody-producing cell with a transformed cell, which results in an immortal, easily cultured cell line that produces a single type of antibody or a *monoclonal antibody*.

The media used to grow animal cells must provide a variety of growth factors, glucose, glutamine, amino acids, specific salts, and vitamins. In some cases, serum from animals (especially mammals) is used. However, serum is expensive, increases the probability of contamination, is undefined in composition, is variable from lot to lot, and complicates the downstream recovery of protein products. In many cases, our knowledge of cellular nutrition has allowed the development of serum-free media, and the use of such media is of increasing importance.

Many potential bioreactor configurations are commercially available for use with animal cells. The reactor design problem centers on providing sufficient oxygen and nutrients and (for anchorage-dependent cells) surface area to achieve high cell densities while minimizing exposure to liquid shear. Also, complete medium utilization and high product concentrations are sought. Designs must minimize the formation of toxic by-products