processing steps necessary to achieve the desired product occur when the protein is expressed in milk, urine, or blood. Nonetheless, transgenic animals will be critical to production of some proteins.

14.3.8. Transgenic Plants and Plant Cell Culture

Proteins, including many complex protein assemblies, such as antibodies and virus-like particles (as vaccines), can be made inexpensively in plants. Transgenic plants offer many potential advantages in addition to cost. Since plant viruses are not infective for humans, there are no safety concerns with respect to endogenous viruses or prions. Scale-up is readily accomplished by planting more acreage. The protein can be targeted for sterile, edible compartments, either reducing the need for rigorous purification or making it an ideal vehicle for oral delivery of a therapeutic protein. Indeed, development of edible vaccines for use in developing countries is being actively pursued.

The disadvantages of transgenic plants are that expression levels are often low (1% of total soluble protein is considered good), N-linked glycosylation is incomplete, and some other mammalian posttranslational processing is missing. While inexpensive, with easy scale-up, it takes 30 months to test and produce sufficient seed for unlimited commercial use. Such long lead times are undesirable. Further, environmental control on field-grown crops is difficult, so the amount (and possibly quality) of the product can vary from time to time and place to place.

While many crops could be used, much of the commercial interest centers on transgenic corn. Some corn products are used in medicinals, so there exist some FDA guidelines (e.g., contamination with herbicides and mycotoxins), and there is considerable processing experience. Production costs vary with degree of desired purity. For high-purity material (95% pure), a cost of about $4 to $8/g can be estimated. For higher-purity material (99%) with full quality assurance and control, a cost of about $20 to $30/g is reasonable. At least two enzymes are being produced commercially from transgenic plants. Large-scale production of monoclonal antibodies (e.g., 500 kg/yr) for topical uses is being considered.

The use of plant cell cultures is also being explored. The primary advantage of such cultures over transgenic plants is the much higher level of control that can be exercised over the process. Plant cell cultures, compared to animal cell cultures, grow to very high cell density, use defined media, and are intrinsically safer.

14.3.9. Comparison of Strategies

The choice of host–vector system is complicated. The characteristics desired in the protein product and the cost are the critical factors in the choice. The dominant systems for commercial production are *E. coli* and CHO cell cultures. An interesting study of the process economics of these two systems for production of tissue plasminogen activator, tPA, has been published by Datar, Cartwright, and Rosen.[†] Their analysis was for plants making 11 kg/yr of product. The CHO cell process was assumed to produce 33.5 mg/l of product, while *E. coli* made 460 mg/l. The CHO cell product was correctly folded, biologically

[†]*Bio/Technology 11*:349 (1993).