shear sensitivity; Chinese hamster ovary (CHO) cells, widely used for protein production, are relatively resistant to shear damage. Gross shear damage where cells lyse (*necrosis*) is obvious. More subtle effects of shear include changes in physiology and, possibly, induction of *apoptosis* or programmed cell death. These more subtle changes can alter apparent growth rates, productivity, and product quality (e.g., due to release of degradative enzymes into the medium).

Hollow-fiber reactors have also been used to provide a high growth surface–volume ratio and, therefore, high cell concentrations. Cells are immobilized on the external surfaces of hollow fibers, and nutrients pass through the tubes. Cell concentrations comparable to those found in tissues can be reached in hollow-fiber reactors. However, the control of microenvironmental conditions inside the reactor where cells are immobilized on fiber surfaces is very difficult, because there is almost no mixing (i.e., a heterogeneous environment). Also, the quantification of growth and product formation is difficult in such a system. However, it is possible to construct the reactor using fibers of known MW cutoff to control the flux of different-molecular-weight products into the effluent stream. The accumulation of some toxic products, such as lactate and ammonium, in the fiber reactors may cause high levels of inhibition. Selection of fiber material (MW cutoff) and flow regime are critical factors for the rapid removal of toxic metabolic products. Hollow-fiber reactors have been used for the production of MAb's from hybridoma cells. Antibody concentrations on the order of 5 to 50 mg/ml have been obtained with this reactor since product is retained by the membrane while medium flows in through the membrane and lower molecular wastes flow out of the cell compartment. Because of severe mass transfer and control problems, this reactor may not be suitable for large-scale production purposes. To overcome some of the difficulties with axial-flow hollow-fiber reactors, radial-flow or cross-flow hollow-fiber units have been developed. Hollow fiber reactors are well suited to perfusion operation with continuous feed. MAb production from hybridomas can be sustained for extended periods (e.g., 100 days), as stationary-phase cells still synthesize product.

The immobilization of mammalian cells in gel beads (agar, alginate, collagen, polyacrylamide) and the use of such systems in a packed- or fluidized-bed configuration are possible. Such immobilization methods and reactor configurations will reduce or eliminate the shear effects on cells. High cell densities make high volumetric productivities possible. However, the control of microenvironmental conditions inside bead particles and the accumulation of toxic metabolic products in beads are potential problems.

A tubular ceramic matrix has been used for the immobilization and cultivation of hybridoma cells. High cell and, therefore, MAb concentrations can be obtained using such systems. The quantification of cell concentration and the control of microenvironmental conditions within the heterogeneous cell culture in ceramic matrix are some of the major difficulties, although these matrices do provide well-defined flow channels. Scale-up of a ceramic matrix reactor may be difficult because of the heterogeneous nature of the system when long tubes are used.

Microencapsulation is another method used for the immobilization of animal cells. Hybridoma cells have been encapsulated within spherical membranes of polylysine–alginate for production of MAb's. Typical capsule size is 300 to 500 μm, and the molecular weight cutoff of these capsule membranes is 60 to 70 kda. Microcapsules operate like small membrane bioreactors, in which very high cell concentrations can be reached ($\sim 10^8$ cells/ml). Using the right capsule membrane with a desired MW cutoff, toxic