Sterility is a prime design consideration for fermenter hardware. Pressurized steam is used for in-place sterilization of the reactor, seals, probes, and valves. The number of openings into the fermenter should be limited to what is essential. A trade-off is necessary between the use of many probes, which improves fermenter control, and of few probes, which improves the chances of maintaining sterility. Small openings are made leakproof with O-rings, while flat gaskets are satisfactory for larger openings. Although small fermenters can use magnetically coupled agitators, industrial-size fermenters have moving shafts that must penetrate into the fermenter. Prevention of contamination due to the entry of foreign organisms through such a shaft is a major challenge in the mechanical design of fermenters. Stuffing-box seals are common on old fermenters, while double mechanical seals are used in newer ones. All surfaces must be smooth. Crevices in the tank surface, pipes, and valves can trap large quantities of particulate organics and contaminating organisms. Such clumps of cells increase the chances for a contaminant to survive the sterilization procedure. Cleanability of all surfaces is important.

Cleaning is generally done "in place," and fermenter design includes spray balls to allow for clean-in-place (CIP) technology. Highly alkaline detergents are often used, and this factor helps dictate the selection of materials. Surfaces, especially in bioreactors for animal or plant tissue cultures, often undergo electropolishing, an electrolytic process that removes the sharp microscopic projections often resulting from mechanical polishing. All ports and valves involved in sampling and injection should be protected with steam-sterilizable closures. The application of a continuous flow of live steam to sample valves is one strategy that is often applied in antibiotic plants.

The same concern for sterility applies to bubble columns and loop (e.g., airlift) reactors. Bubble columns offer distinct advantages for some systems. They are suitable for low-viscosity Newtonian broths; satisfactory mixing may not be possible in highly viscous broths. Bubble columns provide a higher energy efficiency than stirred-tank systems, where by *energy efficiency* we mean the amount of oxygen transferred per unit of power input. An additional advantage often mentioned for bubble columns is that they provide a low-shear environment, which may be a critical consideration with some cells. Cells tend to accumulate at the bubble surface, however, and bubble bursting is highly detrimental to cells. The absence of mechanical agitation also reduces cost and eliminates one potential entry point for contaminants.

Besides having less vigorous mixing capabilities than stirred tanks, bubble column operation is often limited by considerations of foaming and bubble coalescence. Because of bubble coalescence, bubble columns work over a rather narrow range of gas flow rates. The range of appropriate gas flows varies with the nature of the broth. Thus, bubble columns are less flexible than stirred tanks. Partial relief from the problem of coalescence can be found by using multistage columns; each stage (perforated plate) acts to redistribute gas flow. This gas redispersion, however, carries an energy penalty.

Loop reactors have intermediate characteristics between bubble columns and stirred tanks. We will consider primarily the *airlift* system (Fig. 10.1). Here the motion of the gas carries fluid and cells up a draft tube. At the top, gas disengages from the liquid, and the degassed liquid (which is denser than the gassed liquid) descends in the annulus outside the tube. At the bottom of the reactor, the descending fluid again encounters the gas stream and is carried back up the draft tube. Airlift systems can generally handle somewhat more viscous fluids than bubble columns, and coalescence is not so much of a problem. The largest