Although cell lysis is the most obvious result of excess shear, sublytic levels of shear can be important. For a variety of cell lines, it has been shown that attached cells respond to shear by elongating and reorienting themselves to minimize shear stress. Also, the distribution and numbers of cell surface receptors can be altered. These receptors interact directly with components in the medium, such as growth factors, that regulate cell metabolism. Alterations in the production of specific proteins and the rates of DNA synthesis have been observed as responses to shear. This response to sublytic shear complicates scale-up, since the same cells exposed to the same medium, but at different levels of shear, may produce the product of interest at different rates. Also processes, such as N-linked glycosylation, can be altered by shear, resulting in protein products that differ potentially in therapeutic value.

12.3. BIOREACTOR CONSIDERATIONS FOR ANIMAL CELL CULTURE

Mammalian cells are large (10 to 20 μm diameter), slow growing ($t_d \approx$ 10 to 50 h), and very shear sensitive. Moreover, some animal cells are anchorage dependent and must grow on surfaces of glass, specially treated plastics, natural polymers such as collagen, or other support materials; some are not anchorage dependent and can grow in suspension culture. Product concentration (titer) is usually very low (μg/ml), and toxic metabolites such as ammonium and lactate are produced during growth. These properties of animal cells set certain constraints on the design of animal cell bioreactors. Certain common features of these reactors are the following:

1. The reactor should be gently aerated and agitated. Some mechanically agitated reactors operating at agitation speeds over 20 rpm and bubble-column and airlift reactors operating at high aeration rates may cause shear damage to cells. Shear sensitivity is strain dependent.
2. Well-controlled homogeneous environmental conditions (T, pH, DO, redox potential) and a supply of CO_2-enriched air need to be provided.
3. A large support material surface–volume ratio needs to be provided for anchorage-dependent cells.
4. The removal of toxic products of metabolism, such as lactic acid and ammonium, and the concentration of high-value products, such as MAb's, vaccines, and lymphokines, should be accomplished during cell cultivation.

The laboratory-scale cultivation of animal cells is carried out in (1) T-flasks (25 ml to 100 ml) for anchorage-dependent cell lines and for shallow suspension cultures, (2) spinner flasks (100 ml to 1 l) with paddle-type magnetic agitators, (3) roller bottles (50 ml to 5 l) rotating at about 1 to 5 rpm, and (4) trays containing shallow liquid suspension culture. These laboratory-scale reactors are placed in a carbon dioxide incubator at 37°C (5% CO_2-containing air) for the cultivation of mammalian cells. Different steps need to be taken for anchorage-dependent and suspension cells when scaling up animal cell cultures. An example of these steps for one cell line is presented in Fig. 12.5. Reactors with a high surface–volume ratio (microcarrier systems, hollow-fiber reactors, ceramic