isozymes ($E_2$), while the other enzyme ($E'_2$) is fully active. Sufficient activity remains through isozyme $E'_2$ to ensure adequate synthesis of $P_2$.

An alternative approach is *concerted feedback inhibition*. Here a single enzyme with two allosteric binding sites (for $P_1$ and $P_2$) controls entry into the pathway. A high level of either $P_1$ or $P_2$ is not sufficient by itself to inhibit enzyme $E_2$, while a high level of both $P_1$ and $P_2$ will result in full inhibition.

A third possibility is *sequential feedback inhibition,* by which an intermediate at the branch point can accumulate and act as the inhibitor of metabolic flux into the pathway. High levels of $P_1$ and $P_2$ inhibit enzymes $E_4$ and $E_5$, respectively. If either $E_4$ or $E_5$ is blocked, $M_3$ will accumulate, but not as rapidly as when both $E_4$ or $E_5$ are blocked. Thus, intermediate flux levels are allowed if either $P_1$ or $P_2$ is high, but the pathway is inactivated if both $P_1$ and $P_2$ are high.

Other effects are possible in more complex pathways. A single allosteric enzyme may have effector sites for several end products of a pathway; each effector causes only partial inhibition. Full inhibition is a cumulative effect, and such control is called *cumulative feedback inhibition* or *cooperative feedback inhibition*. In other cases, effectors from related pathways may also act as activators. Typically, this situation occurs when the product of one pathway was the substrate for another pathway. An example of control of a complex pathway (for aspartate) is described in Section 4.9.

The reader should pause to consider the differences between feedback inhibition and repression. Inhibition occurs at the enzyme level and is rapid; repression occurs at the genetic level and is slower and more difficult to reverse. In bacteria where growth rates are high, unwanted enzymes are diluted out by growth. Would such a strategy work for higher cells in differentiated structures? Clearly not, since growth rates would be nearly zero. In higher cells (animals and plants) the control of enzyme levels is done primarily through the control of protein degradation, rather than at the level of synthesis. Most of our discussion has centered on procaryotes; the extension of these concepts to higher organisms must be done carefully.

Another caution is that the control strategy that one organism adopts for a particular pathway may differ greatly from that adopted by even a closely related organism with an identical pathway. Even if an industrial organism is closely related to a well-studied organism, it is prudent to check whether the same regulatory strategy has been adopted by both organisms. Knowing the cellular regulatory strategy facilitates choosing optimal fermenter operating strategy, as well as guiding strain improvement programs.

We have touched on some aspects of cellular metabolic regulation. A related form of regulation that we are just now beginning to appreciate has to do with the cell surface.

## 4.7. HOW THE CELL SENSES ITS EXTRACELLULAR ENVIRONMENT

### 4.7.1. Mechanisms to Transport Small Molecules across Cellular Membranes

A cell must take nutrients from its extracellular environment if it is to grow or retain metabolic activity. As we discussed in Example 4.1, which nutrients enter the cell and at what rate can be important in regulating metabolic activity.