The interaction of the field of molecular genetics, especially the part of it termed recombinant DNA technology, with the business of large-scale microbial fermentations is a subject much in the news these days. From the reaction of Wall Street to the recent and prospective public offerings of genetic engineering companies, one would think these companies were in the business of synthesizing the Philosopher's Stone rather than developing methods for getting very large vats of smelly microorganisms to produce biochemicals more effectively.

In a sense, of course, microorganisms can be viewed as a modern-day equivalent of the Philosopher's Stone. Instead of transmuting lead into gold, they transmute other substances of lower value, such as molasses, into compounds of greater value, such as glutamic acid or lysine or vitamin B12 or antibiotics. Much of the current interest in the fermentation aspect of biotechnology derives from the prospect that microorganisms will, in the near future, be able to extend substantially each end of the value spectrum of compounds they act upon and produce. That is, the prospect that microorganisms will be able to economically use substrates of little present value, such as corn stover or old newspapers or various cellulosic waste streams, to make a variety of commodity chemicals and fuels has excited considerable interest. This conference attests to that interest. Similarly, the prospect that microorganisms will soon be able to produce, economically, a range of products of very high value such as interferon, a vast array of enzymes, viral coat proteins for vaccines, etc., has likewise captured the public's imagination. In order for these modern-day Philosopher's Stones to achieve a greater degree of reliability than those of the alchemists, a close collaboration must develop
between molecular geneticists, microbial physiologists, and biochemical engineers.

In this paper, I would like to consider some of the opportunities and some of the problems which will be faced in utilizing genetically engineered microorganisms in large scale fermentations. Throughout the discussion, unless otherwise specified the organism will be assumed to be *E. coli* or closely related *Enterobacteriaceae*. However, it is rapidly becoming the case that certain other species of microorganisms, such as *Saccharomyces cerevisiae*, *Bacillus subtilis*, *Pseudomonas putida*, and several *Streptomycetes* can be genetically engineered as well (1-4).

Figure 1 contrasts what was possible five years ago (left side, Figure 1) with what is possible today (right side, Figure 1) in the area of strain improvement. It shows that the nature of both the opportunities and the problems has changed dramatically in the past five years. Suppose, as illustrated in Figure 1, there is a six-step pathway running from substrate S through intermediates I₁ to I₅ to product P, and that we wish to improve the efficiency with which a microorganism converts S to P. Until recently, the primary techniques available for improving the wild type strain as a production organism were first, mutagenesis and selection or screening for better producers, and second, extensive optimization of physiological parameters affecting product yield. Given adequate resources, these approaches can be very powerful. Obviously, a great deal has been accomplished using them. However, they are very labor intensive and time consuming and thus expensive. In addition, certain desirable goals are beyond the capability of these approaches. For instance, the selection of a fundamentally new enzymatic activity (to allow utilization of a new class of substrate, for instance) in a strain which does not possess some enzymatic activity of the desired type is essentially impossible using the mutagenesis and selection approach.

Molecular genetics, recombinant DNA methodology in particular now offers fundamentally new opportunities for strain improvement. Recombinant DNA methodology in principle allows researchers to use the whole of the genetic information in nature for strain improvement instead of just that fraction of it found within the genome of a single species. This greatly expanded repertoire of enzymatic activities allows strain modification of a sort essentially impossible until recently. Moreover, it allows a directed, rational approach to strain construction using facts about known enzymes and regulatory mechanisms where these are available. Some of the components of such a rational approach are shown on the right hand side of Figure 1.

One obvious approach to improving a wild type strain is to increase the number of enzyme molecules catalyzing the conversion