DIRECTOR'S REPORT

There are times when it is exhilarating, but also humbling, to be a member of a privileged fellowship who collectively call themselves scientists. The year 2000 was such a moment, for we

a matter of time before the concept of sequencing the whole human genome began to be discussed, notably at a meeting organized by Robert Sinsheimer in 1985 at the University of California, Santa Cruz. But the idea of determining the complete sequence of the human genome was controversial, as many biologists saw the cost as being too high. This was a time when grants were particularly difficult to obtain because of limited funding, and there was considerable concern that such an ambitious project could not be completed for technical reasons, even if sufficient funds could be found. During the Cold Spring Harbor Symposium in 1986, Jim Watson brought together some of the leading biologists to discuss the genome sequencing proposal: Was it feasible and, of particular importance, who should fund the considerable cost? Those days now seem far in the distant past, but it was only 14 years ago, a short time in the history of molecular biology. Wally Gilbert's prediction at that meeting that we would all carry our genet-

The first eukaryotic genome to be sequenced was that of the baker's yeast,

have learned from studies on yeast biology during the last few years, it is probable that cell, tissue, and organism physiology will return as a dominant area of investigation but studied now at the molecular level. When this type of analysis is applied to animal studies, it will be possible to see how an organism responds to all sorts of perturbations, leading to an unprecedented understanding of biology and physiology. This is happening at a rapid pace. Already, DNA arrays are being used effectively to study the response of animal cells to extracellular signaling and to drugs used in the clinic. A particularly innovative analysis is under way at Cold Spring Harbor

way too premature talk of human cloning. Knowing our gene sequence, or even a mouse genome sequence, is not going to help overcome all the very considerable technical obstacles that still exist in cloning other mammals. We simply do not understand enough about the methods for producing animals from individual cells. We do not know much about how gene expression programs are reset before development can occur. Clearly, research on cloning should proceed, but knowing the full human genome sequence will only marginally help solve the significant hurdles that exist, and the two areas of science must not get confused when there is discussion about future possibilities.

The achievement of obtaining the sequences of many genomes, including the human genome, is a major milestone in science. Certainly, when the double helix was revealed, it was unimaginable that the entire nucleotide sequence of a genome could be obtained. I still find it humbling to realize that we are in a golden age of biology that will have far-reaching consequences not only for our own science, but also for humankind. At the same time, we should have realistic expectations of what will emerge from these spectacular developments.

On a practical level for most scientists, research has been made much easier because of the reagents that have derived from the genomics age. Clones of genes and fragments of genomes are readily available, as are the predicted sequences of most proteins (we do not yet have the computer tools to predict all protein sequences accurately). These resources have been put to great use, speeding up the pace of biological discovery manyfold. This progress in itself has been a silent revolution, perhaps only appreciated by the scientists actually doing the work. Many of the advantages which have become available to the yeast community during the past six years are now available to those working on human biology, including arrays of human genes, protein analysis by mass spectrometry, and comparisons to the predicted "proteome"—the set of all proteins. It is now possible to analyze the changes in gene expression of the entire set of known human genes in response to physiological changes in cells and tissues. Although it is early in this analysis, new and exciting findings have been reported in the literature. Such experiments have already led to new methods for diagnosing human disease and to the discovery of new targets for therapy. In some cases, the cause of disease has been discovered by the power of being able to compare gene sequences between diverse species, such as those of *roso hila* and human, or even yeast and human.

One of the most interesting aspects of whole genome sequencing in humans is the diversity of sequences that are being uncovered. It is estimated that there is one difference between individuals for each 1300 bases in the human genetic code of 3,000,000,000 bases. This means that we are all about 99.9% identical, something that itself is quite remarkable. But if turned around the other way, then it means that there are about 3 million differences at the primary DNA level between individuals. Most of this variation will not be expressed, but some of it will. This means that individuals will not only have different shapes and sizes—something that we all know about—but also have different probabilities of being afflicted by disease and, when treated, different responses to drugs and other therapy. Such variation will become valuable for predicting how patients might respond to certain drugs, allowing treatments to be targeted to individuals who will benefit from the drugs while avoiding adverse effects of the same drugs in others.

Knowing more about human genomic variation also has the potential to change how we view ourselves as a species. By knowing more about human DNA variation, we will realize that traditional ethnic and cultural boundaries will not be reflected in our DNA, but rather will be purely a human invention with no genetic (and maybe even no biological) basis. If this turns out to be true, and it is really understood by the lay public, then cultural and ethnic differences may not be as dominant in future human endeavor. But, change will occur only very slowly, and this may be an unattainable utopian goal.