



Cancer, AIDS, Huntington's disease, Parkinson's disease—these are some of the most frightening names in pathology today and some of the most formidable foes that science must face on the battlegrounds of medicine. For years now, treatments have been developed, tested, and at best succeeded in slowing the progression of these ailments. Many forms of cancer are becoming more prevalent with time, though, and neurological diseases can only increase in number as people live longer and longer lives. Why hasn't science offered us cures for these diseases yet, and how can we expect to fight them in the future?

According to Samuel Broder, M.D., Executive Vice President and Chief Medical Officer at Celera Genomics, who spoke at Dartmouth College on May 11 for the John P. McGovern, M.D. Annual Award Lectureship on Science and Society, both questions can be answered by the Human Genome Project. Without having the full human genome or the genomes of various infectious microbes available, scientists have been fighting these diseases with “one hand tied behind their backs;” they have been fighting an enemy about which they have only limited knowledge. Imagine having a complete blueprint of your enemy's camp before you attack, says Dr. Broder; that is what genome projects will provide in the future.

Armed with full genomic information scientists will be able to locate and target the areas of greatest vulnerability in microbes. With full *human* genomic information they can target and preserve those areas in which mutations make us more susceptible to cancers and neurological disorders. With the information obtained from genome projects, scientists will be able to fight diseases with both hands.

In fact, this two handed capability is just

around the corner. Dr. Broder believes that Celera Genomics will have the entire human genome sequenced and published by the end of this year, thanks in large part to the ABI Prism 3700—the cutting edge technology being used for “whole genome shotgun sequencing” at Celera. This method of sequencing, says Dr. Broder, basically involves a computer with infinite memory putting together a genetic jigsaw puzzle; tiny pieces are sequenced then matched up to yield the complete picture. With machines like the ABI Prism 3700 working on decoding genomes, we will soon be in a state of daily sequencing and publication of the genomes of free living microbes, giving scientists the edge in fighting infectious diseases—including those caused by microbes that are currently drug resistant.

Once the full human genome is known, tissue specific promoters can be identified and used in gene therapy to prevent certain diseases. Everything from genes to behavior to disease susceptibility will be available to scientists and doctors even before a person is

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born. In this lies some of the biggest controversy over the Human Genome Project. People worry about genetic discrimination and question the wisdom of knowing too much about a person ahead of time. In one example given by Dr. Broder, scientists could predict with very high accuracy when a person would die, just by looking at their genome. Specifically, the number of CAG trinucleotide repeats present in the SCA1 gene involved in spinocerebellar ataxia has a very high correla-

tion to the age at which people with that disease eventually die. Obviously, the gene for this disease has already been deciphered. The question remains, how many more areas in the human

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genome will be discovered that correlate to age of death? Should we know when we are going to die? That is a question for the philosophers. However, it is important to remember that the whole point of deciphering the human genome is to enable scientists to correct these problems early on and thus avoid death—and possibly the philosophical questions—caused by these diseases later in life.

Interestingly, much about human diseases is being revealed by the genome of another animal: *Drosophila melanogaster*. The fruit fly’s entire genome has been sequenced, and within it scientists have encountered many previously unknown counterparts to human disease. The conservation of these counterparts over millions of years of evolution is amazing.

For example, mutations in the PAX6 gene in fruit flies and its correlates in mice and humans all cause blindness. In addition to PAX6, gene correlates involved in heart disease, Huntington’s, Parkinson’s, many forms of cancer, and diabetes have all been found in the fruit fly. Experiments on these correlates should someday produce gene therapies or other treatments for humans suffering from these diseases.

Even without gene therapy, knowing the full human genome could reveal information about disease that would allow humans to avoid becoming sick. Phenylketonuria (PKU), for exam-

ple, is a disease in which a mutation in the gene coding for an enzyme in the metabolism pathway of phenylalanine causes a buildup of phenylalanine in the blood, which then leads to mental retardation and, in many cases, epilepsy. Once it was realized that this disease was the result of a defective metabolic pathway, treatment became very simple: avoid eating foods containing phenylalanine. So, a simple diet change (along with early detection of the disease) allows PKU patients to live virtually normal lives. There must be other diseases that result from metabolic pathway defects, and mapping the full human genome will tell us what those diseases are. Imagine being able to avoid Alzheimer’s Disease just by refusing certain foods. That may be possible within the next couple of years.

At the very beginning of his lecture, Dr. Broder mentioned that, as director of the National Cancer Institute from 1989 to 1995, his favorite type of lecture to give was the one in which he talked about progress: cancer being cured or tumors being removed. Certainly his lecture at Dartmouth College was one on progress. His enthusiasm for the potential benefits of deciphering the complete human genome was obvious, and one could not help but walk away from Filene auditorium that night with a fair measure of optimism for the fight against diseases that even one year ago seemed unstoppable. The human genome will be deciphered soon, and then we will see if Dr. Broder is right to be so enthusiastic about what Celera Genomics has been spending so much time working on in recent months. At the very least, we will be no worse off than we were last year for having sequenced the human genome. On the other hand, we may be facing an era of medical progress unmatched by anything in history. ■