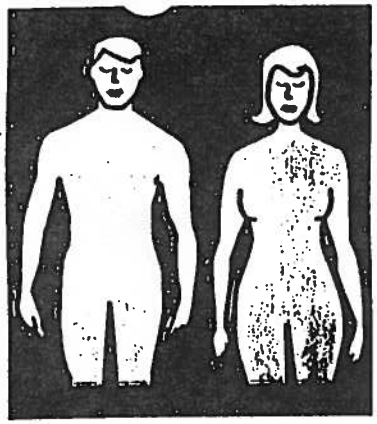
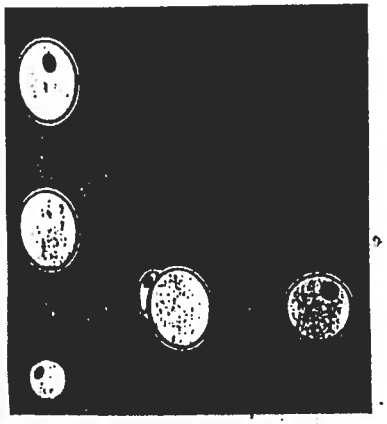
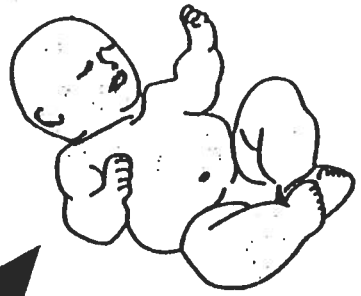


Man and Woman

In Vitro Fertilization



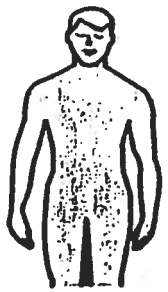
Somatic Cell
Nuclear Transfer



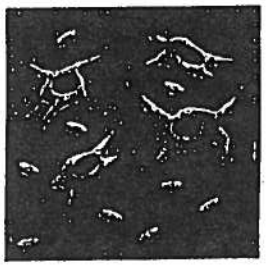
New Human Being

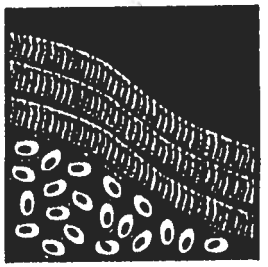
Early
Embryonic
Cells

Specialized
Cells



Adult





Therapeutic
Tissue

E S S A Y

Charles Krauthammer

Of Headless Mice . . . and Men

The ultimate cloning horror: human organ farms

LAST YEAR DOLLY THE CLONED SHEEP WAS RECEIVED with wonder, titters and some vague apprehension. Last week the announcement by a Chicago physicist that he is assembling a team to produce the first human clone occasioned yet another wave of Brave New World anxiety. But the scariest news of all—and largely overlooked—comes from two obscure labs, at the University of Texas and at the University of Bath. During the past four years, one group created headless mice; the other, headless tadpoles.

For sheer Frankenstein wattage, the purposeful creation of these animal monsters has no equal. Take the mice. Researchers found the gene that tells the embryo to produce the head. They deleted it. They did this in a thousand mice embryos, four of which were born. I use the term loosely. Having no way to breathe, the mice died instantly.

ED GABEL FOR TIME

Why then create them? The Texas researchers want to learn how genes determine embryo development. But you don't have to be a genius to see the true utility of manufacturing headless creatures: for their organs—fully formed, perfectly useful, ripe for plundering.

Why should you be panicked? Because humans are next. "It would almost certainly be possible to produce human bodies without a forebrain," Princeton biologist Lee Silver told the London *Sunday Times*. "These human bodies without any semblance of consciousness would not be considered persons, and thus it would be perfectly legal to keep them 'alive' as a future source of organs."

"Alive." Never have a pair of quotation marks loomed so ominously. Take the mouse-frog technology, apply it to humans, combine it with cloning, and you are become a god: with a single cell taken from, say, your finger, you produce a headless replica of yourself, a mutant twin, arguably lifeless, that becomes your own personal, precisely tissue-matched organ farm.

There are, of course, technical hurdles along the way. Suppressing the equivalent "head" gene in man. Incubating tiny infant organs to grow into larger ones that adults could use. And creating artificial wombs (as per Aldous Huxley), given that it might be difficult to recruit sane women to carry headless fetuses to their birth/death.

It won't be long, however, before these technical barriers are breached. The ethical barriers are already cracking. Lewis Wolpert, professor of biology at University College, London, finds producing headless humans "personally distasteful" but, given the shortage of organs, does not think distaste is sufficient reason not to go ahead with something that would save lives. And Professor Silver not only sees "nothing wrong, philosophically or rationally," with producing headless humans for organ harvesting; he wants to convince a skeptical public that it is perfectly O.K.

When prominent scientists are prepared to acquiesce in—or indeed encourage—the deliberate creation of deformed and dying quasi-human life, you know we are facing a bioethical abyss. Human beings are ends, not means. There is no grosser corruption of biotechnology than creating a human mutant and disemboweling it at our pleasure for spare parts.

The prospect of headless human clones should put the whole debate about "normal" cloning in a new light. Normal cloning is less a treatment for infertility than a treatment for vanity. It is a way to produce an exact genetic replica of yourself that will walk the earth years after you're gone.

But there is a problem with a clone. It is not really you. It is but a twin, a perfect John Doe Jr., but still a junior. With its own independent consciousness, it is, alas, just a facsimile of you.

The headless clone solves the facsimile problem. It is a gateway to the ultimate vanity: immortality. If you create a real clone, you cannot transfer your consciousness into it to truly live on. But if you create a headless clone of just your body, you have created a ready source of replacement parts to keep you—your consciousness—going indefinitely.

Which is why one form of cloning will inevitably lead to the other. Cloning is the technology of narcissism, and nothing satisfies narcissism like immortality. Headlessness will be cloning's crowning achievement.

The time to put a stop to this is now. Dolly moved President Clinton to create a commission that recommended a temporary ban on human cloning. But with physicist Richard Seed threatening to clone humans, and with headless animals already here, we are past the time for toothless commissions and meaningless bans.

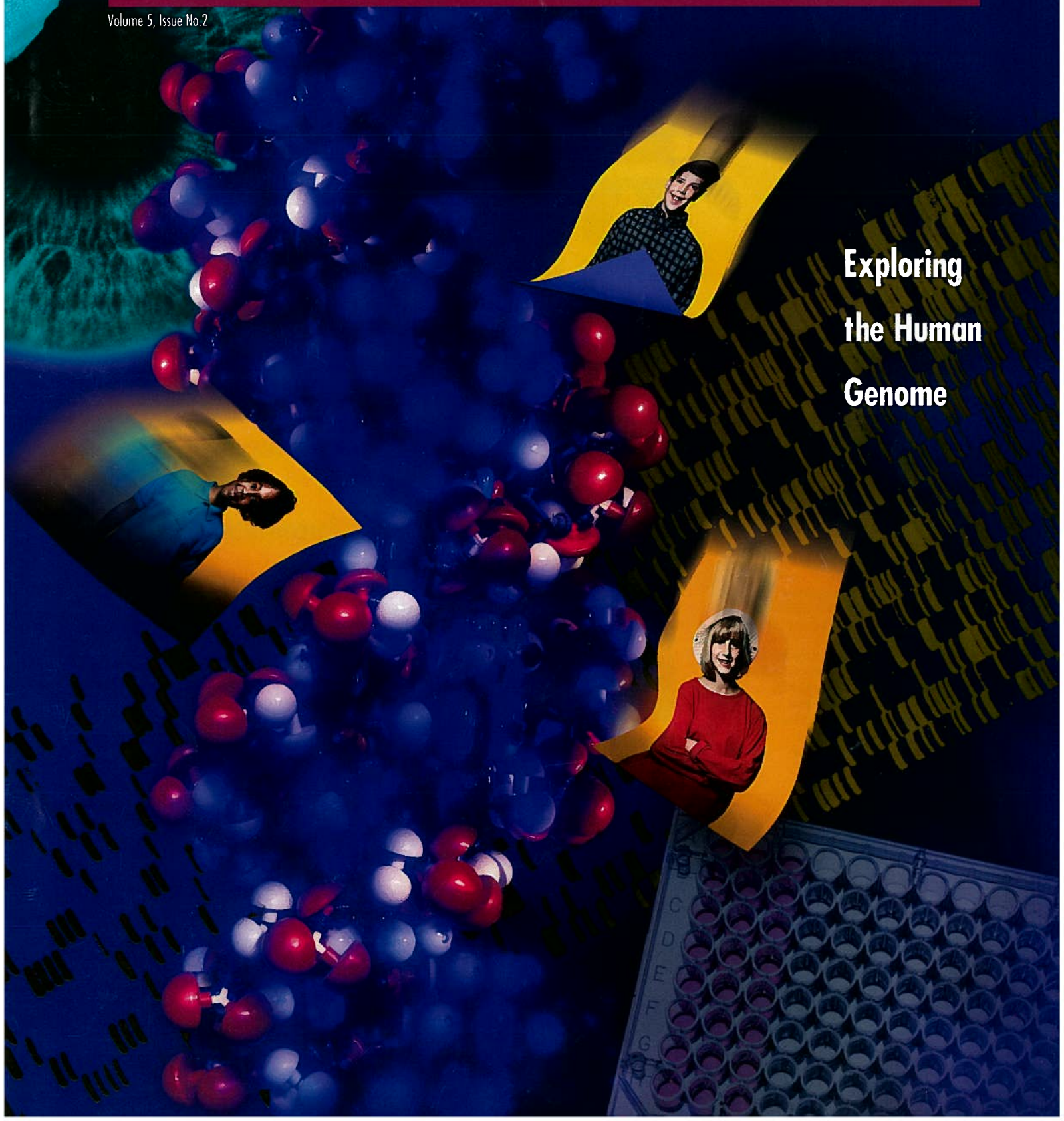
Clinton banned federal funding of human-cloning research, of which there is none anyway. He then proposed a five-year ban on cloning. This is not enough. Congress should ban human cloning now. Totally. And regarding one particular form, it should be draconian: the deliberate creation of headless humans must be made a crime, indeed a capital crime. If we flinch in the face of this high-tech barbarity, we'll deserve to live in the hell it heralds. ■

YOUR WORLD

BIOTECHNOLOGY & YOU

a magazine of biotechnology applications in healthcare, agriculture, the environment, and industry

Volume 5, Issue No.2



Exploring the Human Genome

YOUR WORLD
BIOTECHNOLOGY & YOU

Volume 5, Issue No. 2

Your World/Our World describes the application of biotechnology to problems facing our world. We hope that you find it an interesting way to learn about science and engineering.

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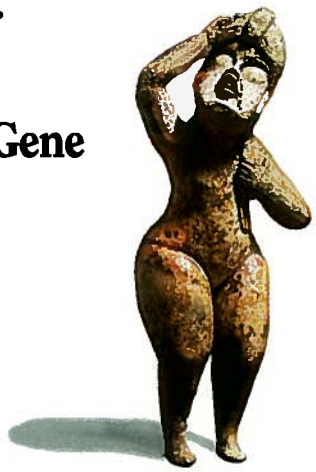


Cover: *Exploring the genome requires some of the items on the cover – and more. Can you tell what these items are? (Answers on page 23.)*

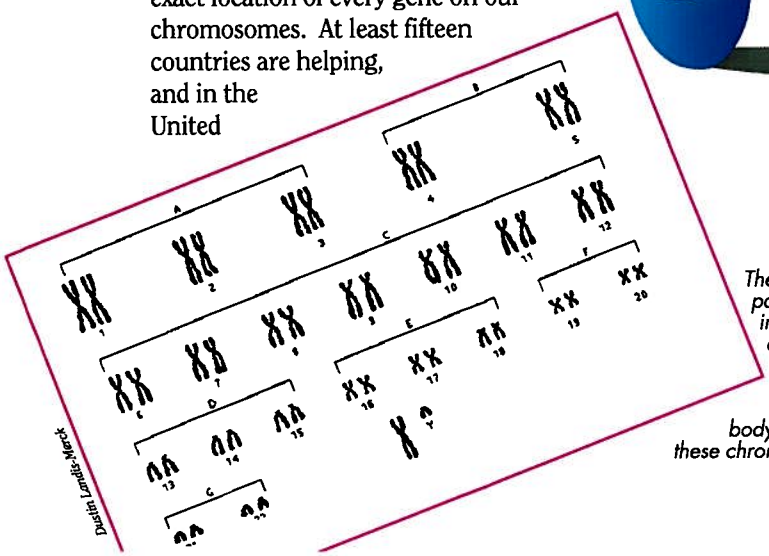
Odyssey into Ourselves

The *Human Genome Project* will find all human genes and provide tools to understand their functions.

You look like every other person – two eyes, a nose, a mouth. Yet you are unique as well. You are like others because every human being has the same set of about 100,000 genes. You are unique because each of these genes has many variations. You have inherited a unique set of variations from your parents.

Your genes determine what you look like, some diseases you might get, and many, many other things about you. Understanding what these genes do in the body can help us learn a lot about human biology and health. Eventually, we may even understand one of the great mysteries of life: how a human being grows from a single cell.

Until recently, the effort to find and study genes has been extremely difficult, slow, and costly. To speed up that process, scientists have launched an ambitious exploration called the *Human Genome Project*. (The word "genome" is a combination of the words "gene" and "chromosome," and it refers to our genetic information.) The project's goal is to "map" the exact location of every gene on our chromosomes. At least fifteen countries are helping, and in the United States, the project is funded by the Department of Energy and the National Institutes of Health. The project began in 1990 and is expected to end in 2005.



Dustin Lundis-Merck

The human genome has 23 pairs of chromosomes, including either an "XX" chromosome pair (for females) or an "XY" chromosome pair (for males). Every cell in your body has a complete set of these chromosomes.

What will happen after 2005? The *Human Genome Project* will probably raise more questions than it will answer, and it will open doors to new and exciting areas of research that your generation can study throughout the next century.

In this magazine, you will read about the science behind the exploration of the human genome, such as the structure of DNA (the "information molecule" that contains genes) and how genes cause physical traits by producing proteins. You will learn a few techniques for mapping chromosomes and how rapid improvements in supporting technologies have dramatically increased the pace of gene mapping. You will see how the discovery of genes that play a role in three human conditions (a genetic disease, a cancer, and the common affliction of being overweight) may lead to a revolution in medicine and health. You will also consider the difficult questions of how the discovery of genes will affect us as individuals and as a society. Join us as we begin this odyssey into ourselves. ■

What are ten ways you are the same as everyone else in your class? What are ten ways you are different?

the Human Genome Project: 1990 - 2005

In 1990 when the *Human Genome Project* began, finding genes on a chromosome was like exploring a vast continent with only a few landmarks. When the project is finished in 2005, every nook and cranny of that continent will be fully mapped.

Why Try to Understand the Human Genome?

Human beings suffer from over 4,000 genetic diseases caused by faulty genes. In addition, such common conditions as cancer, heart disease, allergies, and arthritis are caused by an interaction of genes and the environment. Exposure to radiation, asbestos, smoke, etc. can trigger genetic changes in our cells that could cause disease. By fully understanding genes, we will be able to test for the presence of disease forms of genes, develop new techniques for preventing disease, develop new medicines and treatments, and even correct faulty genes.

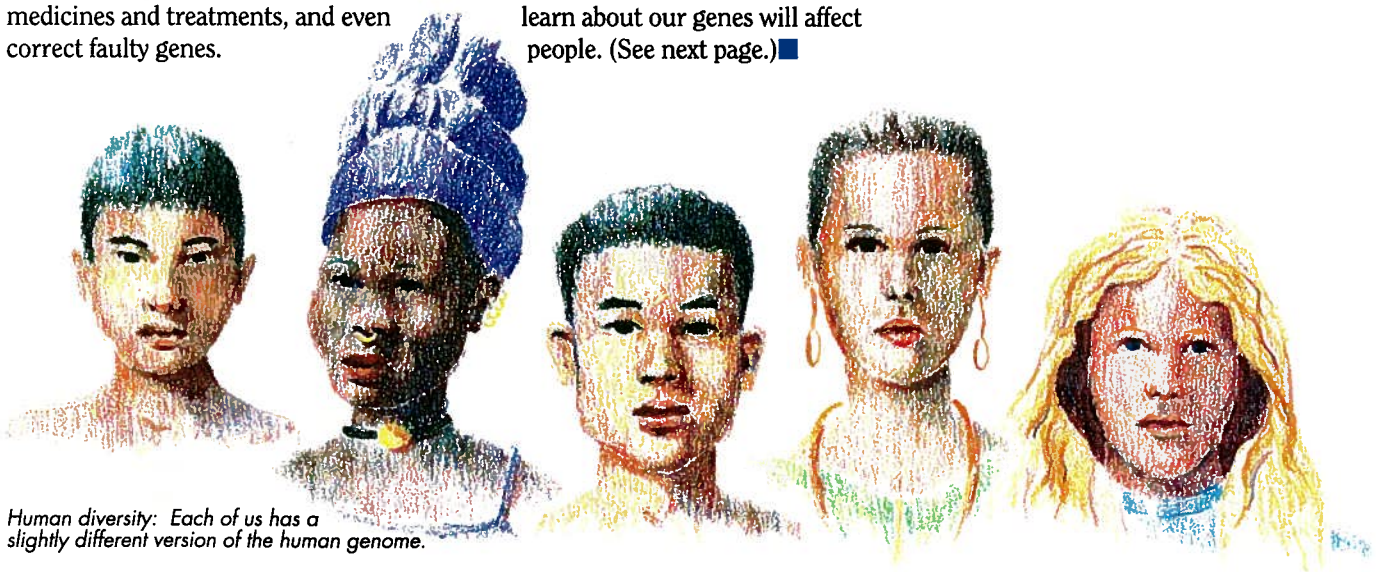
The *Human Genome Project* will provide detailed maps of the genes on each chromosome.

In its first five years, the *Human Genome Project* (HGP) has sped up the discovery of genes even faster than scientists had hoped. Regrettably, though, we are also finding that this new knowledge can be a double-edged sword. For instance, we are often able to test for a disease gene long before we can treat the disease. Would you want to know you were going to get an untreatable disease? Would your family want to know? In addition to mapping genes, the HGP is studying how the ability to learn about our genes will affect people. (See next page.)■

Whose Genome?

There is really no such thing as the human genome. Rather, there are billions of human genomes, one for each person who has ever lived. While they are similar, they are not identical.

The *Human Genome Project* has collected DNA samples from volunteers around the world. These samples represent a mix of people of both sexes and many ethnic and geographical backgrounds. Researchers are now developing a *representative* map showing the areas common to all of us (over 99.9% of the genome) and the places where variations occur. For instance, everybody has a slightly different variant of the gene for eye color, but it does the same basic job and it is in the same location on everyone's genome.▼



Human diversity: Each of us has a slightly different version of the human genome.

A QUESTION OF ETHICS

Ethical, Legal, and Social Implications (ELSI)

ELSI researchers are studying how the powerful new knowledge about our genes will affect people. They will form ethical guidelines by listening to what people like you and your family think and how you make decisions. There are no right or wrong answers to these ethical questions, and many "experts" disagree about the best solution. However, there are a few basic values or principles that help guide their decisions – and probably yours, too. Some of these principles are:

1) Autonomy: You should be able to decide for yourself whether to have a genetic test to learn about what genes you have, and you should not be tested against your will. But who decides for a child or teen?

2) Access to Information and Informed Consent : You should be able to get important information about what a genetic test can and cannot tell you.

3) Privacy and Confidentiality: You have the right to keep the results of a genetic test to yourself. You also have the right not to learn the results of a test. Should you keep private something that affects other people's health and well being?

4) Benefits and Risks: Knowing the results of genetic tests should do more good than harm, such as allowing you to get better medical care. But what if there is no treatment or prevention for a condition or a disease? Is knowledge, without the ability to act, harmful?

5) Justice: Genetic tests should be accessible to everyone. But who will pay, and for what kinds of tests? Can information about genetic tests be used fairly? Will laws that protect us from discrimination apply to genetic conditions?

Sometimes one of these principles conflicts with another, as you will read about later. Then people have to decide which principle is more important in that situation.

When is a Difference a Disease?

Until recently, a child born deaf learned to live as a deaf person. Someday, genetic deafness may be correctable. Should people be forced to hear, or should society accept deafness as "normal" in some people?

Some conditions are unpleasant, painful, or debilitating, so we call them "diseases." Other conditions, such as being very short or overweight, might seem disadvantageous in some societies. If genetic research leads to "treatments" for these conditions, will they be considered "diseases" by that society?

As we learn more about our genome, we will find that every one of us has some genes that are not "normal." The *Human Genome Project* may force us to redefine the concepts of "disease" and "treatment." It will be up to all of us to balance the effort to relieve human suffering caused by disease with the goal of respecting the rich diversity of humanity.

. . . the Human Genome Project identified a gene controlling strength or someone's idea of "beauty" or "intelligence"? How might this information be used? Could it do more harm than good?

How to Get There: "Enabling" Technologies

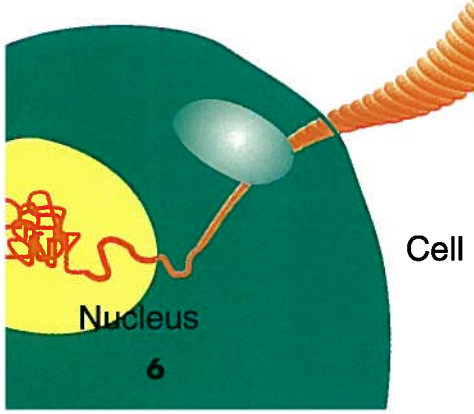
For centuries, people wanted to walk on the moon, but until we had the technology to get there, such exploration was impossible. Similarly, the *Human Genome Project* has to make progress in several technologies to reach its goals. While some research groups are mapping the chromosomes, others are developing faster and easier techniques for mapping. Some are developing techniques for working with the fragile DNA molecules that contain genes. Others are building machines and robots that analyze the order – or sequence – of the information in DNA. Still others are developing powerful computer programs that piece together these DNA sequences into a whole picture of the genome. Other computer programs are building enormous databases to store and analyze genetic information – and to make it available to researchers around the world. These "enabling" technologies make scientists "able" to reach their goals. You can read about some of these technologies on pages 10-15.▼

THE STRUCTURE AND FUNCTION OF DNA

DNA Primer
(See Illustration)

1. **DNA (deoxyribonucleic acid) is found in the nucleus of human cells.**
2. **DNA has four bases – adenine (A), thymine (T), cytosine (C), and guanine (G) – arranged along double strands of sugar-phosphate molecules.**
3. **The bases on the two strands are complementary, with A always opposite T and C always opposite G. These combinations are called *complementary base pairs*.**
4. **The double-stranded DNA molecule has the shape of a ladder. The base pairs are the rungs, and sugar-phosphate molecules are the rails. This ladder twists up tightly, forming a "double helix" (helix means "spiral").**
5. **DNA is *duplicated* or copied when its strands separate and new bases bind to their complements on each strand. An enzyme, DNA polymerase, helps add bases to build a new strand.**
6. **The order or sequence of bases in the DNA molecule carries the message or "meaning" of DNA's instructions. (See next article.)**

This illustration shows what you might see if you could unwind DNA and watch as it is duplicated.



The study of the human genome is the study of DNA, the molecule that makes up genes.

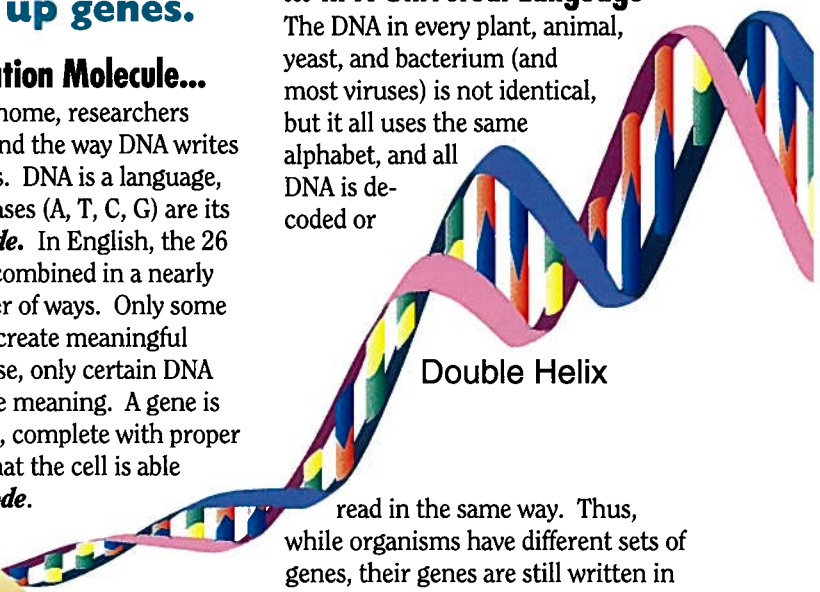
The Information Molecule...

To map the genome, researchers must understand the way DNA writes its instructions. DNA is a language, and the four bases (A, T, C, G) are its alphabet or ***code***. In English, the 26 letters can be combined in a nearly infinite number of ways. Only some combinations create meaningful words. Likewise, only certain DNA sequences have meaning. A gene is like a sentence, complete with proper punctuation that the cell is able to read or ***decode***.

mqtp lkm ghdpnr
definitely not a sentence
I am happy.
definitely a sentence
Yu mak prough.
Looks like a sentence, but is it?

... In A Universal Language

The DNA in every plant, animal, yeast, and bacterium (and most viruses) is not identical, but it all uses the same alphabet, and all DNA is decoded or read in the same way. Thus, while organisms have different sets of genes, their genes are still written in the ***universal code*** – just as two books can tell different stories but still use the same language.



Furthermore, different organisms have many similar genes. If you compared a book about a cat to one about a dog, you might find sentences with many of the same words, such as those describing how dogs and cats walk on four paws. Likewise, the DNA "book" of two mammals will have many related genes.

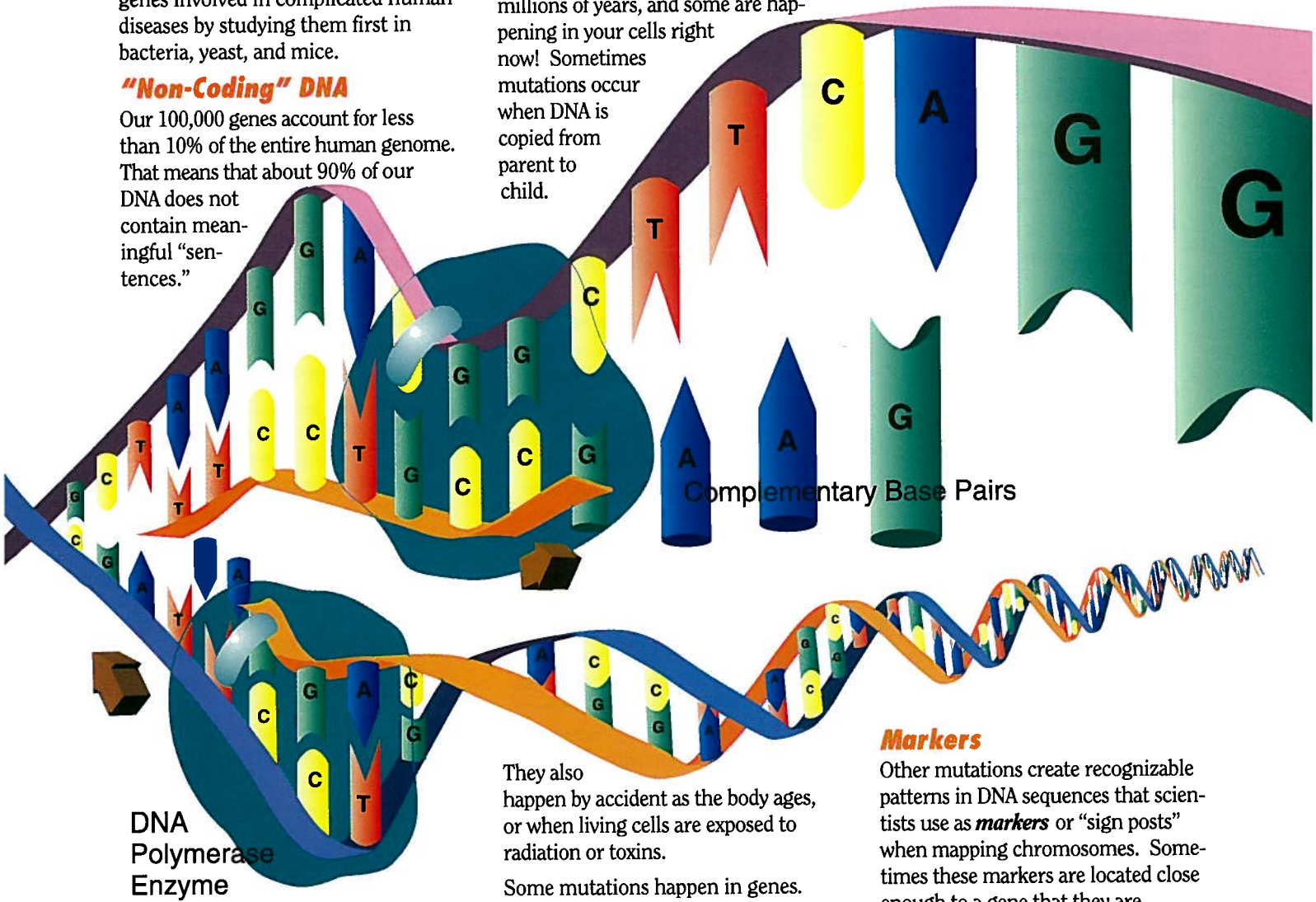
These similarities are very useful to science. We can learn about human genes by studying organisms with fewer genes and less DNA. Imagine that bacterial DNA is a children's book telling a very simple story about a cat. Before reading a complicated technical book about cats, you could

As you read this issue, look for ways genetic researchers use these characteristics of DNA: the complementary binding of base pairs, specific order or sequence of bases, and the ability to be copied.

learn the basics by reading the children's story first. In the same way, scientists are learning about genes involved in complicated human diseases by studying them first in bacteria, yeast, and mice.

"Non-Coding" DNA

Our 100,000 genes account for less than 10% of the entire human genome. That means that about 90% of our DNA does not contain meaningful "sentences."



Imagine an encyclopedia with sentences sandwiched between nonsense sequences like "pond oooo gt dggtg." It would be hard to read! In a similar way, genes are sandwiched between sections of ***non-coding*** DNA whose function we do not understand. The huge amount of non-coding DNA makes finding genes difficult, sort of like looking for a needle in a haystack when the needle looks just like the hay!

Mutations

Sometimes small changes or mistakes are introduced into a DNA sequence. These changes are called ***mutations***. They account for many of the differences in our genomes, and for much of the diversity among species.

Mutations have been happening over millions of years, and some are happening in your cells right now! Sometimes mutations occur when DNA is copied from parent to child. They also happen by accident as the body ages, or when living cells are exposed to radiation or toxins.

Some mutations happen in genes. Such mutations can change the way a gene reads in the same way changing letters, punctuation, or spacing can change the meaning of a sentence:

The boy went up the hill.
th eboy we ntup Theh ill,
The boy bent up the hill.

A mutation in a gene might have no effect on a person, or it might cause a gene to be unreadable or to say something with a different meaning. Some of theses changes in meaning can cause genetic diseases.

Markers

Other mutations create recognizable patterns in DNA sequences that scientists use as ***markers*** or "sign posts" when mapping chromosomes. Sometimes these markers are located close enough to a gene that they are "linked" to the gene. That is, the gene and the marker are usually inherited together when passed from parent to child. Scientists can use these linked markers to identify the presence of a gene even if the gene itself has not been found. (See page 16.)

How many is a billion? The human genome is about three-billion (3,000,000,000) bases long. Can you picture three billion of anything? If you live for three-billion seconds, how long will you be alive?

Genes, Proteins & Genetic Disease

A Genetics Primer

- There is more than one variety of most genes. Some genes have disease varieties and healthy varieties.
- The variants of the gene can be dominant, recessive, or co-dominant.
- Some traits are caused by a single gene, others by a combination of genes.
- Genes are arranged in a specific order along chromosomes.
- Each of us has 23 pairs of chromosomes. We inherit one chromosome in each pair from each parent.
- The chromosomes we inherit from our mother contain a combination of genes from her parents. Likewise, our dad's chromosomes contain a combination of genes from his parents.
- This recombination of genes leads to the infinite variety of individuals.
- Genes located on different chromosomes are inherited independently of each other.
- Genes (and markers) located near each other on the same chromosome are often inherited together, so they are *linked* when passed from parent to child.

As you read this magazine, you will learn about ways that linked genes are used in mapping the human genome.

Genes are the "blueprints" or "recipes" for the proteins that cause physical traits. Small mutations in a gene can change the protein and the trait.

The DNA Sequence of Genes Defines the Function of Proteins

Once scientists identify a gene, they must next learn to "read" it so they will understand how it functions in the body.

They do this by studying the "protein" the gene codes for. Each gene is a "recipe" for a different protein. (See illustration on page 9.) Some proteins provide the structure for cells, others produce hormones or signals for cells, and still others help read and translate DNA into more proteins.

Small mutations in a gene can cause changes in the protein, just as words dropped or rearranged in a sentence can change the meaning. These changes can interfere with the way a cell works and sometimes lead to a disease.

For example, *cystic fibrosis* (CF) is the most common genetic disease in this country, but scientists did not understand what caused its many symptoms until they identified and studied the CF gene in 1989. Scientists learned that a small change in the CF protein interferes with the transfer of salt and water in and out of the cell, causing mucus to thicken. This thick mucus is the most life-threatening symptom of CF because it leads to lung infections. Now scientists are trying to add copies of healthy varieties of the gene to the lung cells so these cells can produce the correct protein and function properly. This kind of treatment is called *gene therapy* because the genes themselves are being used as treatment.

DNA Probes: Testing for Genes

Understanding which changes in a gene cause a disease can help doctors diagnose the condition in patients and then begin proper treatment.

Suppose a very young child has serious respiratory infections. Does the child have just a short-term health problem? An immune disease? Cystic fibrosis? Knowing the answer might help the child receive better medical treatment. Now that the CF gene is known, scientists have developed a ***DNA probe*** to test for that gene in a sample of the patient's DNA.

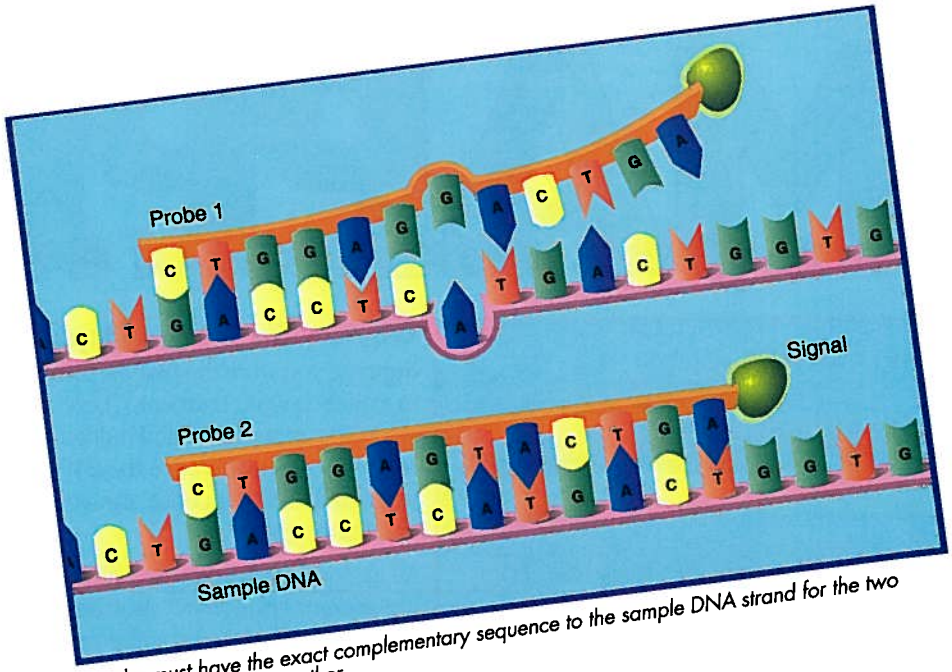
To make a probe, scientists take advantage of the structure of DNA, specifically the way the two strands bond together as complements. (See page 6.) First, they pinpoint a section of the disease gene that contains a sequence that is different from the healthy gene. Scientists make a probe for that section by stringing together complementary bases that correspond perfectly to the sequence in this particular section of the gene. Then they attach a chemical that will cause the probe to glow under certain conditions.

Scientists next take a blood sample from the child, extract the DNA, and make many copies of this DNA so they can study it. They separate the double strands of the

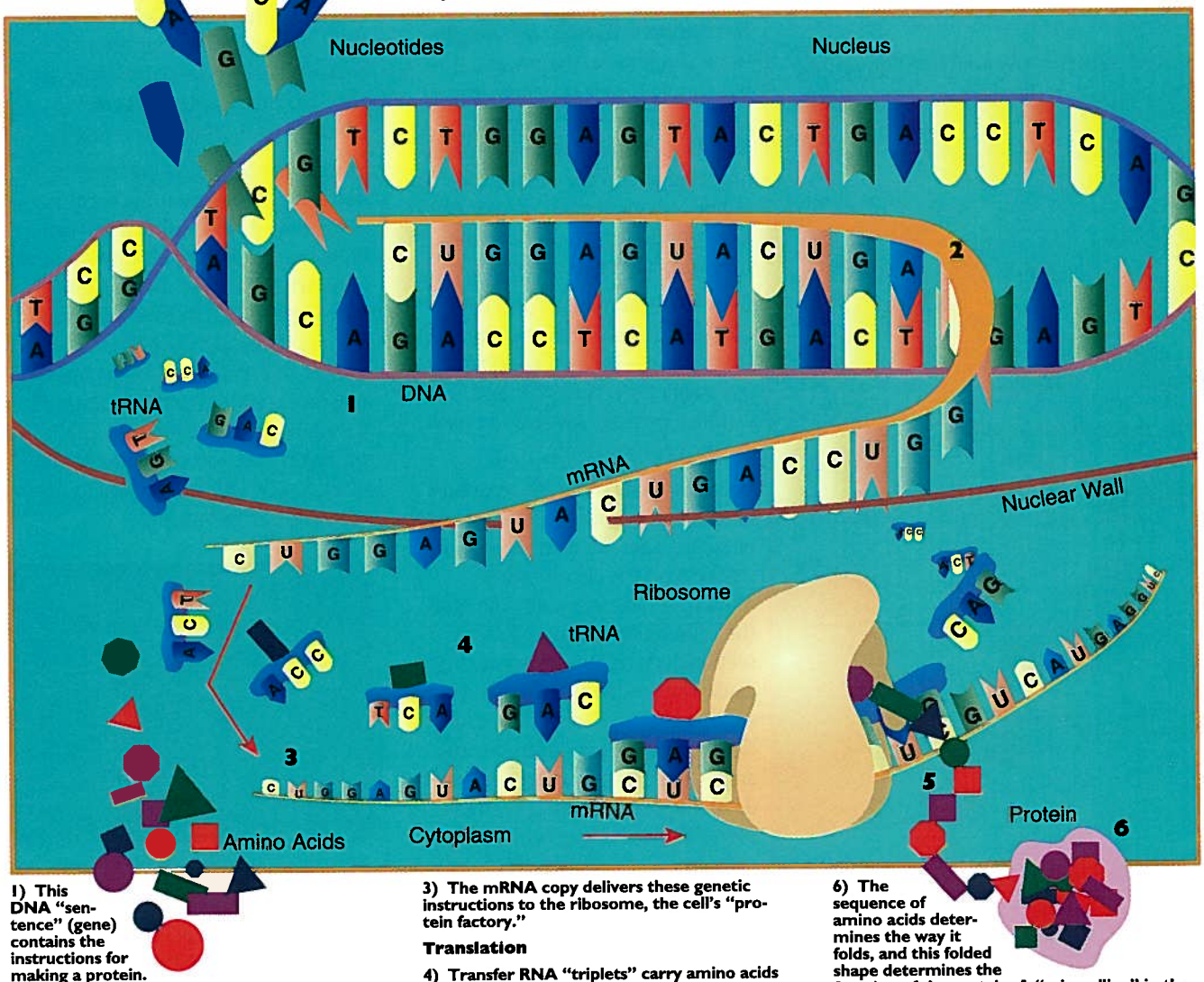
If scientists are looking for a gene that affects the lung cells, why do they look for it in the DNA from blood cells?

DNA and add the single-strand probe. If the probe finds its complement on the DNA strand, it will bind to it. Otherwise the probe will not bind and will be washed away. If the scientists detect a glow on the "probed" DNA, they know that the disease-causing section of DNA is definitely present.

Probes not only help diagnose a genetic disease in a patient, they are also used for mapping genes. (See next page.)



A probe must have the exact complementary sequence to the sample DNA strand for the two strands to bind to one another.



1) This DNA "sentence" (gene) contains the instructions for making a protein. The DNA separates into two strands. One strand serves as a "template" or pattern for making the protein.

Transcription

2) A messenger copy (mRNA) of the gene's sentence is made and edited. RNA bases line up in the order of their complements on the DNA strand. RNA, ribonucleic acid, uses the base "U" (uracil) instead of T.

3) The mRNA copy delivers these genetic instructions to the ribosome, the cell's "protein factory."

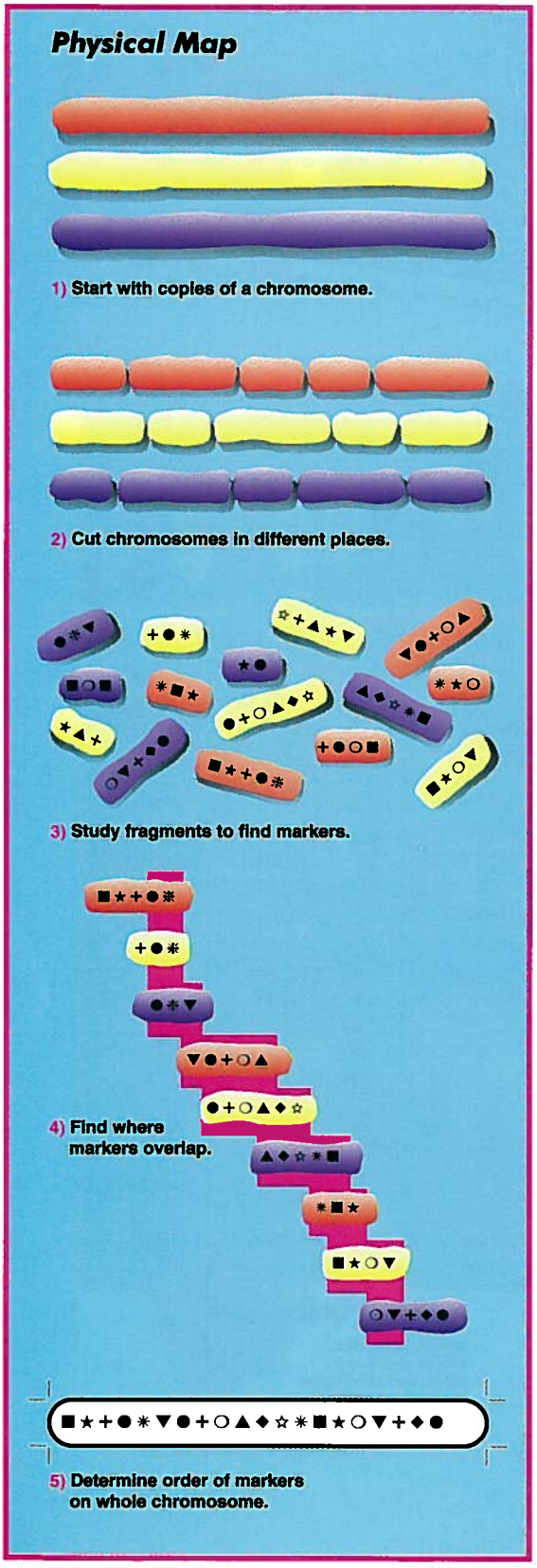
Translation

4) Transfer RNA "triplets" carry amino acids to the ribosome. The type of amino acid is specified by the three bases on the tRNA. The tRNA molecules bind to three complementary bases on the mRNA strand.

5) As they pass through the ribosome, the amino acids are linked together to form a chain. Thus, the original DNA sequence is "translated" into a sequence of amino acids. The completed chain is a protein.

6) The sequence of amino acids determines the way it folds, and this folded shape determines the function of the protein. A "misspelling" in the DNA can change the shape and function of the protein and may cause a genetic disease.

MAPPING
the great unknown of a chromosome



Why Do We Need a Map?

Suppose you were the first person to explore a vast continent. There are rivers, mountains, and hidden treasures – but where are they? If you could find them once, can you find them again?

All explorers create maps, including genome "explorers." As people learn more about a particular area, the maps become more accurate and detailed.

Different Kinds of Maps

What if you knew there was a treasure in a cave on a hill near a city somewhere in the United States? To find it, you might use a map that shows the hills of the region, or one that shows state and city boundaries, or one showing the roads leading to the cave.

Genome explorers can also use different maps to find their genetic "treasurers"– genes. *Genetic linkage maps* show the order and distance between genes and markers on a chromosome.

Physical maps show the structure of a chromosome in different levels of detail. Less detailed maps show markers on the chromosome. More detailed maps show more of the DNA base sequence of some sections on the chromosome. (As discovery progresses, there may be variations in map detail from section to section, similar to the way ancient maps show more accurate detail in areas that have been explored more thoroughly.) Mapping a chromosome requires both genetic linkage and physical maps.

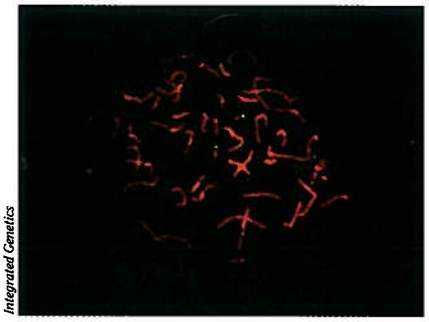
How to Map a Chromosome

1) Genetic Linkage Maps

First, researchers study the way genetic markers are inherited through families. The more often markers are inherited together, the closer together they must lie on a chromosome. Markers that are not inherited together very often must lie farther apart. Researchers use this information to make a genetic linkage map that shows the distance between markers and their order on the chromosome, as you can do on the next page.

However, a genetic linkage map doesn't necessarily tell you which chromosome the markers are on. It is like knowing that Baltimore lies closer to Washington, D.C. than to New York City, without knowing which country these cities are in.

Sometimes scientists can track a marker to a chromosome because they know it is linked to a marker known to be on that chromosome. Otherwise, they can create a *probe* (see page 9) for a marker's DNA sequence. They add the probe to a sample of prepared chromosomes. The probe will show the location of the sequence, revealing not only which chromosome is home to the marker, but also the general location on the chromosome.



Integrated Genetics

A marker on chromosome 21: A probe shows where a marker lies on the chromosome. (Notice the two green dots in the middle.) By using probes for other markers, scientists could create a rough physical map of this chromosome.

2) Physical Maps with Markers

To learn more about the chromosome itself, scientists work on physical maps. Scientists cannot study a

whole chromosome at one time because it is too long and too full of information (150 million bases). They can analyze only small fragments (1,000 to 30,000 bases) at a time. Therefore, scientists cut the chromosome into tiny pieces for study. But when they do that, they lose the order of the pieces. Finding that original order is like working on a jigsaw puzzle with each piece the same color and no edge pieces! To solve this problem, scientists use many copies of the same chromosome and cut each copy in different places. They find recognizable DNA markers on each piece and then look for places where the fragments share some of the same markers. Using these overlapping sections, computers then figure out the original order of the chromosome, as you can do at the right.

3) Physical DNA Sequence Maps

The final steps in physical mapping are examining the actual DNA sequence for each fragment and then compiling the sequence of the entire chromosome. Developing computers and programs that can perform this task is one of the great challenges of the *Human Genome Project* and has led to a whole new field called "Informatics." (See page 14.)

Using Maps to Find Disease Genes

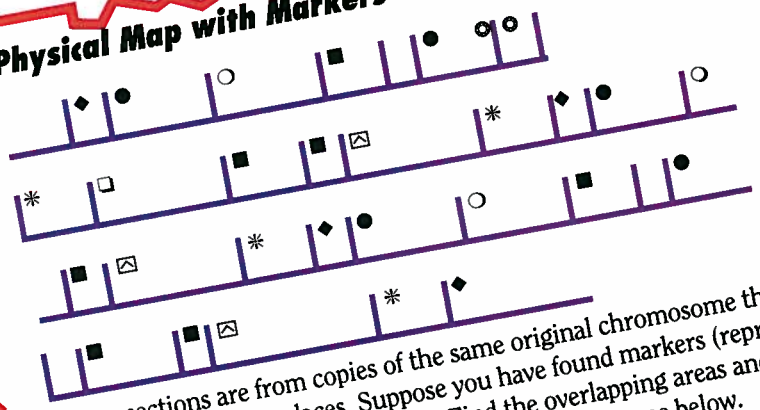
Scientists use maps to find disease genes hidden among three-billion bases. Genetic linkage maps tell scientists which area of the chromosome to examine. Physical maps help find the disease gene itself. Then scientists can prepare probes for genetic testing, and they can study the protein the gene makes. This knowledge may lead to better ways of treating the disease. But before you learn about these efforts, you can read about new technologies that make mapping possible.

Genetic Linkage Map

Suppose four markers (represented by red, green, yellow, and orange) are located on the same chromosome. The numbers below show how often they are inherited together per 1000 cases. The more often they are inherited together, the closer they are physically. Lay out the relative position of the markers on the chromosome below starting with green on the left.

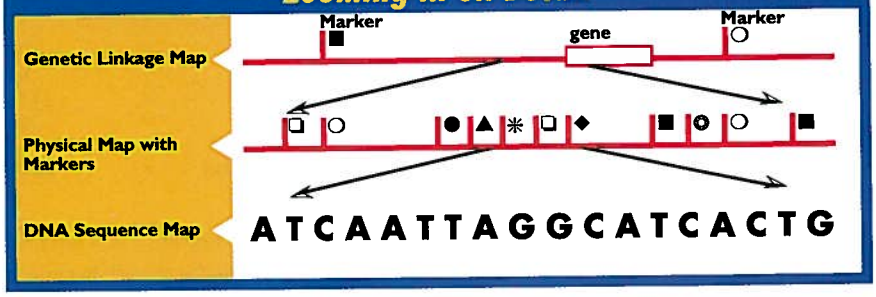
	Known Relationship of Markers	Times inherited together out of 1000
1	Green & Orange	150
2	Red & Green	4
3	Green & Yellow	200
4	Yellow & Orange	950
5	Orange & Red	20
6	Yellow & Red	10

Physical Map with Markers



These sections are from copies of the same original chromosome that were cut in different places. Suppose you have found markers (represented by symbols) on each section. Find the overlapping areas and show how the markers are arranged on the chromosome below.

From Genetic Linkage Maps to Physical Maps Zooming in on Detail



PCR: The Accidental Discovery of Something Obvious

Clever new techniques for working with DNA have made advances in genetic research possible. One of these techniques, called PCR, takes advantage of the way DNA is copied.

Kary Mullis was driving to his cabin in northern California one weekend in 1983, but he kept thinking about his work as a molecular biologist making DNA probes. Having a large supply of probes is essential to genetic research. Researchers often have only a tiny DNA fragment to work with, and yet they need to perform many tests on that fragment. Kary knew the pace of research was slowed by the tedious process of making copies of DNA fragments for study. He wanted to find a faster, easier way.

He was thinking about how the DNA polymerase enzyme might help solve this problem. In the cell, this enzyme plays an important role in duplicating DNA. In his laboratory, Kary used it to make DNA copies for probes, one at a time. Kary suddenly realized he could take advantage of the enzyme's natural ability and make many copies of DNA at one time. He was so excited that he almost drove off the road!

How is PCR like a chain letter?

How PCR Multiplies DNA

Each cycle of PCR doubles the number of copies. If a cycle takes four minutes, here is how the number of copies grows over time.

Cycle	Doubles the Number		Number of Copies	Minutes
start	2 (initial double helix)	=	2	0
1	2x2	=	4	4
2	2x2x2	=	8	8
3	2x2x2x2	=	16	12
4	2x2x2x2x2	=	32	16
5	2x2x2x2x2x2	=	64	20
6	2x2x2x2x2x2x2	=	128	24
7	2x2x2x2x2x2x2x2	=	256	28
8	2x2x2x2x2x2x2x2x2	=	512	32
9	2x2x2x2x2x2x2x2x2x2	=	1,024	36
10	2x2x2x2x2x2x2x2x2x2x2	=	2,048	40
11	2x2x2x2x2x2x2x2x2x2x2x2	=	4,096	44
12	2x2x2x2x2x2x2x2x2x2x2x2x2	=	8,192	48
13	2x2x2x2x2x2x2x2x2x2x2x2x2x2	=	16,384	52
14	2x2x2x2x2x2x2x2x2x2x2x2x2x2x2	=	32,768	56
15	2x2x2x2x2x2x2x2x2x2x2x2x2x2x2x2	=	65,536	60
16	2x2x2x2x2x2x2x2x2x2x2x2x2x2x2x2x2	=	131,072	64
17	2x2x2x2x2x2x2x2x2x2x2x2x2x2x2x2x2x2	=	262,144	68
18	2x2x2x2x2x2x2x2x2x2x2x2x2x2x2x2x2x2x2	=	524,288	72
19	2x2x2x2x2x2x2x2x2x2x2x2x2x2x2x2x2x2x2x2	=	1,048,576	76

What is the next cycle? How many copies would there be after one hour and forty minutes?

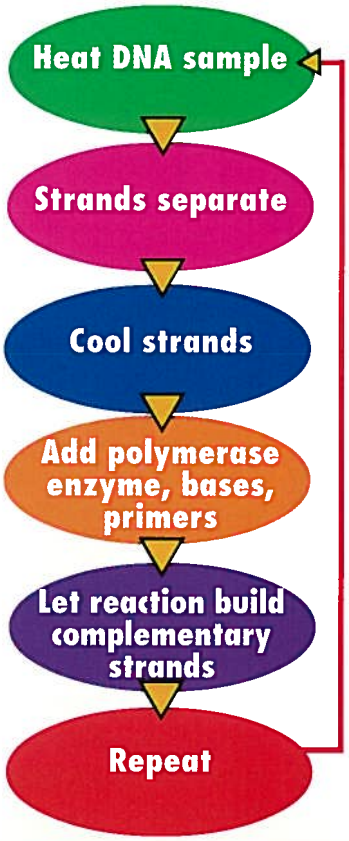
Note: The growth in the number of copies is "geometric" while the growth in time is "arithmetic."

Concentrating again, he reviewed his idea. You heat a double strand of DNA to make the strands separate. When the strands cool, you add the polymerase enzyme, a mixture of the bases (A, T, C, and G), along with DNA *primers* (which start or "prime" the polymerase enzyme reaction). The polymerase builds a complementary strand of DNA for each original strand, so you have two identical copies of double-stranded DNA. You have doubled the number of DNA sections. What if you heated these two sections and repeated the process? And then did it again?

Kary knew that the products of such a "loop" grow exponentially, like a chain letter. In this case, they would grow by the power of two: 2, 4, 8, 16, 32, 64, and so on. Two to the power of ten was...1024!

Kary stopped the car to check his calculations. By heating and cooling the DNA and polymerase in a similar "loop" process, he could get ever larger numbers of the same DNA fragment. By the time Kary reached his cabin, he was calling this process the *polymerase chain reaction* or PCR. His only concern was that someone might have done it already.

Back at work, he researched all the experiments done with DNA polymerase. No chain reaction. He told his friends and colleagues about it. "That's nice," they seemed to think. "Another of Kary's nutty ideas." He planned a simple experiment in a single test tube to tell him whether or not the idea could work. The result: it worked!

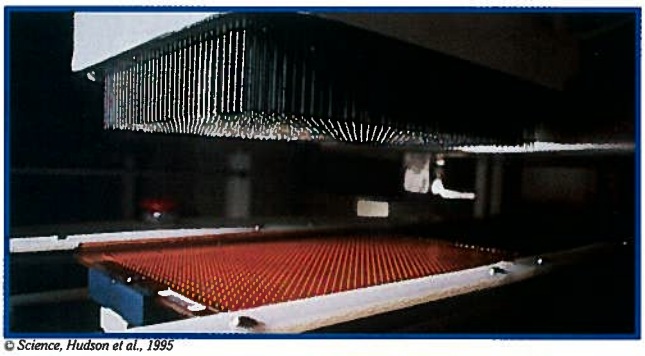


Since then, the uses of PCR have grown almost as fast as the chain reaction. The *Human Genome Project* would not be possible without the ability to make millions of low-cost copies of a DNA section within hours. For example, scientists need many copies of a chromosome to study and to construct maps. (See pages 10 and 11.) In addition, once a gene is found, scientists make copies or "clones" for gene libraries so researchers around the world can use them. In other research areas, scientists now can take a tiny DNA fragment from a mummy or a drop of blood at a crime scene and make enough copies to analyze. PCR is now so essential to scientific research that his off-the-wall idea earned Kary Mullis the Nobel Prize in Chemistry in 1993. Like many great discoveries, PCR now seems so simple and obvious that many a scientist must be saying, "Why didn't I think of that!"■

Careers Galore

People from many fields are involved in the *Human Genome Project*. Find out more about what people do in these fields. Do any of these seem like future careers for you?

- Molecular genetics
- Classical genetics
- Computers
- Robotics
- Chemistry
- Optical physics
- Cell biology
- Medicine/physiology
- Mathematics
- Ethics
- Genetic counseling
- Photo imaging



The "Genomatron," a super-duper PCR machine that made possible the most complete physical map of the entire human genome in 1995. This detail shows a 1,536 head pipette that dispenses DNA to be tested.

Genetic Linkage Map from page 11

green yellow orange red

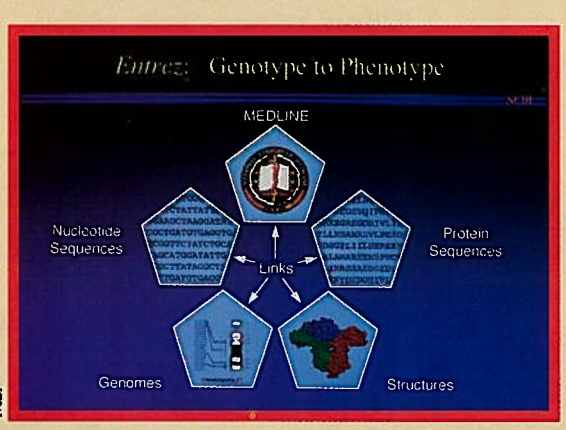
Physical Map with Markers from page 11

Answers from page 19: #3) Marker B. #4) Yes.

The *Human Genome Project* needed new computer tools to analyze and share the huge amounts of information being collected on the DNA of many organisms.

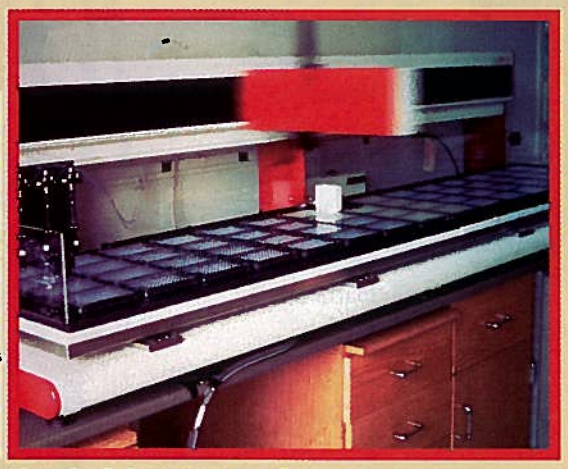
Informatics & Automation

Mark Boguski enjoyed reading about the fictional computers used to identify the ancient dinosaur DNA in Michael Crichton's book *Jurassic Park*. He was curious about the 28 lines of DNA code that were supposed to be from *T. rex*. "What is it really?" Mark wondered. "Had Crichton cleverly 'mutated' a chicken gene to mimic 270 million years of evolution from an ancestor species?"



NCBI

This photo shows a "home page" from one of the genome databases on the World Wide Web.



Robert Strausburg, National Center for Human Genome Research

This robot helps prepare tests for mapping DNA markers, filling pipettes with tiny volumes of liquids.

To find out, Mark turned on his computer, went "on line" to the World Wide Web, plugged in that sequence, and within two minutes learned that it was really DNA from a common bacterium.

Any of us with access to the Internet could do the same. Researchers around the world can enter a DNA sequence they just decoded in their laboratories. Within minutes, a program called BLAST (Basic Local Alignment Search Tool) checks every sequence contained in its database. It looks for exact matches, close matches, and distant matches, like finding the letters "CAT" in the words "catnip," "catch," "locate," and "scratch."

Scientists can then analyze these matches. In language, two sentences with several important words in common might be about a similar subject. Likewise, if a new DNA sequence has patterns similar to a known gene, it might have a similar function, such as producing a blood protein or duplicating DNA.

Computer programs can find similarities among genes from different species, even if they are billions of years apart on the evolutionary scale. These discoveries have led to new understandings of human biology. (See pages 20-23.)

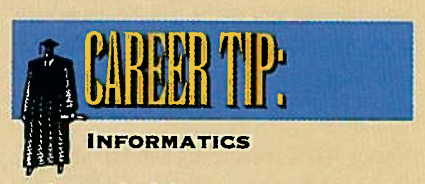
BLAST is one of several programs in the public database called GenBank. Another national database called Genome Sequence Data Base, also banks DNA sequences, and one called Genome Database contains mapping and other important data. Every day, one of these sequence databases might process 30,000 search requests and enter 1,500 new sequences. As of March 1996, these databases contained 690,000 DNA sequences made up of 471 million base pairs representing 9,200 species.

Finding a match to a new sequence is just the beginning. Other computers help analyze what the genes do and these explanations are added to databases for future "search and match" operations. So far, we understand the function of less than 10% of human genes, so there is still much work to be done!

What To Do With a Brand New Sequence?

If BLAST finds no matches to known genes, researchers can use a program called GRAIL (Genome Recognition Analysis Internet Link). GRAIL can check the DNA sequence to see if it is part of an unknown gene. In language, we can tell if a series of words forms a sentence because we recognize the beginning capital letter, spaces between words, and punctuation marks. In a similar way, GRAIL knows the punctuation and format common to genes, and so it can tell if a sequence is part of a gene. If it is, researchers will try to figure out what function the gene has in the body.

GRAIL's first success was locating the gene for the disease *adrenoleukodystrophy,* which was featured in the 1993 movie *Lorenzo's Oil*. After scientists could not locate this gene through genetic linkage procedures, GRAIL "predicted" the sequence of this gene. Researchers used this prediction to make probes that eventually pin-pointed the gene.



At the end of the *Human Genome Project,* researchers will have accumulated a treasure trove of DNA sequences and information about some of their functions. Yet no one could use all this valuable information without computers to help interpret it. "Informatics specialists" use computers to plan and run experiments, and to collect, manage, store, distribute, and analyze data.

Automated Sequencers: Bringing Biology Labs into the Industrial Age

How do laboratories come up with these new DNA sequences? It used to be very slow and difficult. In 1985, scientists grew DNA in bacterial clones, used sterilized toothpicks to move it from one plate to another, added chemicals, processed it, and loaded it into sequencing machines. Researchers could burn out after six months of this boring, repetitive work, and they were likely to make mistakes.

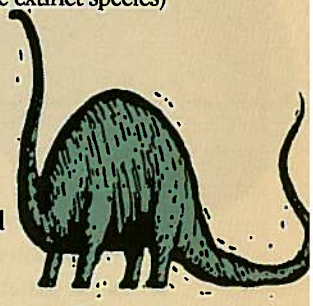
Today, in some labs dedicated to sequencing, robots prepare the DNA and shuffle it around the lab, and sequencing machines are automatic. The results are faster and more accurate, freeing the researchers for more creative work in understanding the significance of the data. It now takes only days to do what once took years.

Automation has also reduced research costs. In 1985, sequencing cost about $10 a base pair. In 1995, the most automated labs had reduced this cost to 39¢. Scientists hope to see costs of 10¢ per base pair by 1998. With three-billion base pairs in the human genome, every cost reduction saves a lot of money!■

What is the cost of sequencing the three-billion base pairs of the human genome at:

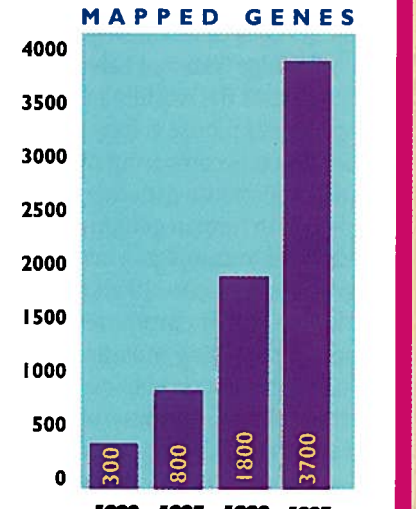
$10/bp
$0.40/bp
$0.10/bp

We Won't Bring Dinosaurs Back



While the film *Jurassic Park* raised an interesting possibility (cloning dinosaur DNA and recreating the extinct species) such a thing simply cannot really happen. Scientists have successfully extracted DNA from fossilized mosquitoes, but the DNA is too fragmented to reconstruct the animal's complete genome. Fortunately, recreating animals is only a goal of science fiction, not of the *Human Genome Project.* A more likely outcome of the HGP will be a better understanding of how some species have evolved from the dinosaurs.▲

The Genome Information Explosion



The Human Genome Project has greatly increased the rate at which genes are being mapped to chromosomes. We still have a long way to go to map all 100,000 genes.

Career Profile: Lisa Stubbs, Molecular Geneticist

Lisa Stubbs is a Senior Scientist at Oak Ridge National Laboratory in Tennessee.

After Lisa Stubbs earned her Ph.D. in molecular biology from the University of California at San Diego, she did post-doctoral research on mouse genetics. "We worked with mouse genes," Lisa recalls, "because mice are easier to study than humans, yet they are very similar. If you ignore their tiny body size and fur," Lisa explains, "their heart, lungs, kidneys, etc. are almost exactly like ours. And for every mouse gene we find, there is usually a human gene that does almost the same thing. We can study one mouse gene at a time and learn a lot about how it functions in both mice and people."

Lisa now heads a research group at the Oak Ridge National Laboratory, which houses the world's largest experimental mouse colony. Part of her group is comparing maps of human and mouse genomes. They worked with human genome researchers to complete a comparative map of Chromosome 19 and are now working on other chromosomes. Others are studying mutations in mouse genes that lead to conditions such as epilepsy, deafness, blindness, and skeletal and muscular disorders. These researchers are trying to find the genes and understand how the mutations affect the health of the animal.

"It's a good time for this research because there are so many tools available," Lisa states. "And also, the human genome community now realizes the importance of mouse genomics to their own field!"■

Huntington's Disease: An Unhappy Destiny

Graphic of HD marker

Steve Uzzell

Nancy Wexler studies family trees to see how Huntington's disease is inherited through these families.

In 1692, several women from one family were accused of being witches during the Salem witch trials. They were believed to be witches because their limbs shook uncontrollably. Of course, they were not witches. Some historians believe these particular women may have inherited a condition called Huntington's disease (HD) from a common ancestor. If so, they may have had the symptoms – tremors, personality change, depression, memory loss – caused by the HD gene that destroys the nervous system. Through the centuries, many HD victims have been seen as insane, alcoholics, or criminals. Even if diagnosed correctly, there is no treatment or relief for the suffering.

Symptoms of HD do not begin until middle age, and by that time, many people with HD have already had children. Each child has a 50% chance of inheriting the disease because it is caused by a dominant gene, meaning it takes only one copy of the gene to cause a trait.

In the 1960s, a clinical psychologist named Nancy Wexler knew this suffering well because her mother had HD. Would she get it, too? She would if she had the gene, but no one knew what the HD gene was or where to find it.

Nancy led a search for the HD gene that took her to a village of 3,000 people on Lake Maracaibo in Venezuela. HD usually affects only 1 in 20,000 people, but at Lake Maracaibo 1 in 3 have the disease. They are all descendants of one ancestor who came to Venezuela in the 1860s.

The discovery of this large family helped find the HD gene. To track down an unknown gene, researchers compare DNA samples from as many related people as possible. They compare the inheritance of *markers* with the inheritance of the disease.

Certain patterns in DNA sequences create genetic markers. Scientists use these markers to identify the presence of a disease gene even if the actual gene is still unknown. When a marker

is always present in a person with HD and not in an unaffected individual, the marker is linked to the disease gene. (See activity on page 18.)

In 1981, Nancy sent thousands of DNA samples from the families to a research lab. In 1983, researchers rejoiced. They had found a few markers linked to the gene! However, it took another ten years to find the gene itself. Many laboratories around the world joined the search. This international effort became a model for the *Human Genome Project.*

Scientists hope the discovery of the HD gene will finally lead to a treatment for the disease. Unfortunately, they do not yet understand the function of the unusual protein the gene makes, so this goal is out of reach for now.■

A QUESTION OF ETHICS

An Oracle without Hope - Yet

Once markers for Huntington's disease were found, younger people with HD parents could be tested to see if they inherited the HD gene. A test could end years of uncertainty and anxiety for those who do not have the gene. Those with the gene could decide whether or not to have children and could plan for future medical and financial care. However, many people are choosing not to get tested. They would rather live with hope than with the certainty of a fate they cannot avoid.

In addition, a positive result could lead to discrimination by schools, employers, health insurers, and others. The person with the gene might find doors closed to a career, health care, and even marriage.

Nancy Wexler has been working on the ethical and social issues of the *Human Genome Project.* She will not tell anyone whether or not she has been tested for HD. She believes people have a right to know about their genes, and they have a right not to know. Most importantly, though, they have a right to privacy: they do not need to share information about their genes with anyone: employers, insurers, spouses, or other family members.

Discussion:
Rights in Conflict

Do people have a right to know if a genetic disease is in their family?

Suppose your grandmother had Huntington's disease, and your father is her child. Your father gets tested and tells you he has the HD gene. What do you now know about your own fate?

What if your father will not tell you the result of his test, but you want to know? As a minor, should you be able to get yourself tested? Suppose your father does not get the test but you do. What if you do have the HD gene? Should you tell him? Should you tell your older sibling who is planning to get married and have children?

Suppose your parents want to have you tested even though you might become dangerously depressed if you knew you had the fatal gene. Do your parents have the right to get you tested in the same way they can have your infected tonsils taken out?

Would you want to marry someone if if you knew he or she had the HD gene?

An Ancient Human Drama

"It is but sorrow to be wise when wisdom profits not."

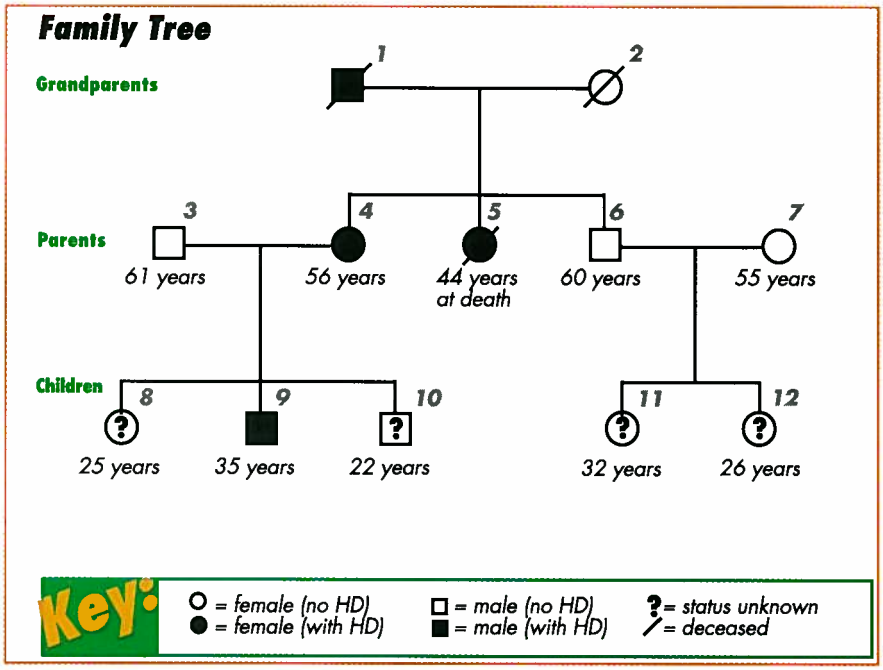
Oedipus Rex *by Sophocles*

The classical Greeks believed in oracles, messages from the gods about a person's unavoidable fate. Many Greek plays and myths concern the tragedies of people who try to avoid their fate. Read these stories and ask yourself: How is a genetic test for an incurable disease like an oracle in these stories? How is it different? What if people could change their fate – would they want to hear what the oracle said?▲

ACTIVITY:

Finding a Marker for Huntington's Disease

Imagine that you work in the research lab where Nancy Wexler sent the DNA samples of Venezuelan families with Huntington's disease. How would you analyze these samples? First you would examine the family trees *(pedigrees)* that Nancy constructed after speaking with family members. The family trees will show how the disease is inherited. Here is what you might see:

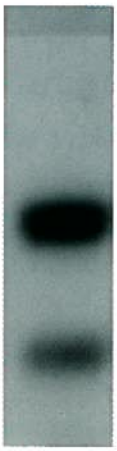


In diagrams of family trees, a "T" reflects a marriage, and a vertical line represents a parent/child relationship.

Questions:

1) Why is the status of some of the children unknown?

2) Is there a chance that persons 8 or 10 have the HD gene? What about persons 11 or 12?



Autoradiogram: The markers appear as bands.

Integrated Genetics

Preparing the Markers

Your laboratory runs genetic tests on the DNA samples collected from the family. You try to find markers with inheritance patterns that match the inheritance of the disease as shown in the family tree.

First, you make probes for markers at various places in the genome. You "label" the probes so they will appear as bands in a special photograph called an *autoradiogram*.

Persons 10, 11, and 12 have not given DNA samples to the lab because they do not want to know if they will get HD later in life. Person 8 does want to know. Your research will give her the answer.

Matching the Pattern of Markers to the Disease

Your lab analyzes two markers and arranges each according to the family tree (see page 19). Every person has two forms of each marker which appear as bands in their "autoradiogram"; one form (band) is inherited from the father, and the other is inherited from the mother.

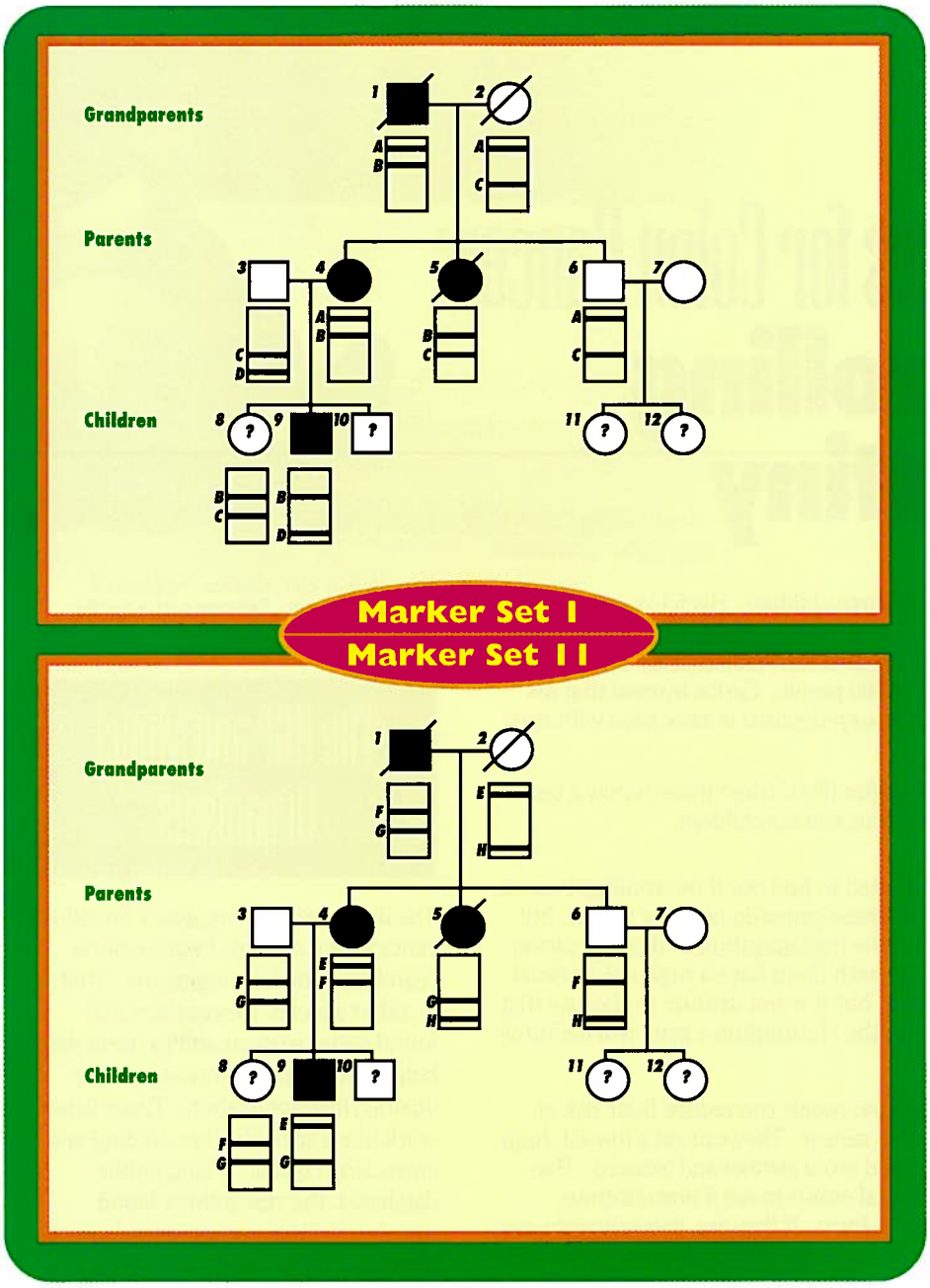
For example, for marker I grandparents 1 and 2 pass a different combination of marker forms to their children (4, 5, and 6). Daughter 4 must have inherited "A" from her mother and "B" from her father. She marries husband 3, who has different forms of the marker from his parents. Notice that sometimes unrelated people can have same form of a marker, just as both 1 and 2 have the "A" form.

When researchers study different markers, they do not know at first whether any of them are linked to the inheritance of the disease.

Marker I on page 19 is a ***linked marker*** that shows this pattern; all family members with HD have one form of the marker in common. Unaffected children of a parent who has HD inherit the other marker form from that parent.

Marker II is an ***unlinked marker***, so it shows no regular pattern: no single form of the marker always appears in family members who have HD. Researchers have to wade through many sets of unlinked markers before they find one that is linked.

To find the linked form of marker I, look for a band that always appears in people who have the disease and never in older parents who do not have it.



Question:

3) Which form of marker I is linked to the inheritance of HD in this family?

Using the Marker

Once your lab has identified a marker for the gene, you can tell if younger people inherited the HD gene.

Question:

4) Will person 8 get HD when she grows up?

Answers on page 13.

Science now allows us to diagnose Huntington's disease. Perhaps your generation of scientists will develop a treatment for it.

Career Profile: Brian Silven, DNA Laboratory Coordinator

Integrated Genetics

Brian Silvan has a bachelor's degree in microbiology from the University of Rhode Island and is certified in medical technology. He worked in clinical microbiology laboratories before joining Integrated Genetics, Inc.

As the DNA Laboratory Coordinator for Integrated Genetics, Inc. in Massachusetts, Brian Silven is in charge of genetic testing for real people with real lives and real problems.

"People make hard decisions based on the results of our testing," explains Brian, "so I feel a tremendous responsibility to make sure the tests are valid. I feel bad when a test shows they have a gene for a serious disease. I have no idea what it would be like to know you will get a serious genetic disease. I wonder how I would deal with that information. That's why genetic counselors are so important. Also, if a prenatal test shows that a fetus has a genetic disease, I feel very sad for the parents, but I'm glad genetic testing makes that information available to them. It helps them prepare emotionally for dealing with the disease."

For Brian, the hardest part of genetic testing is knowing how important the results are to people. "You need an internal confidence in your ability and judgment, and you can't allow that confidence to be shaken."

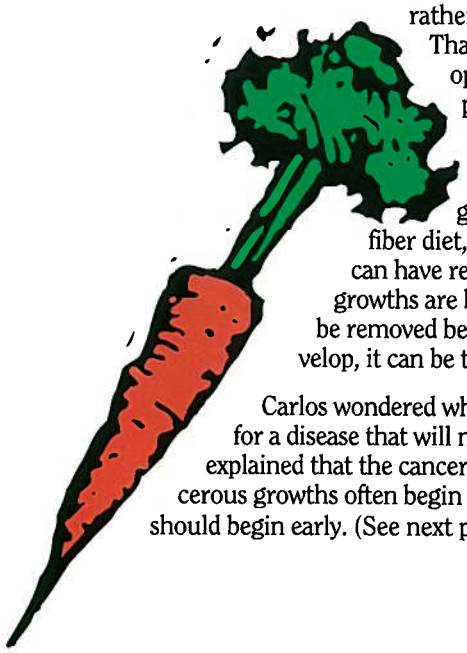
Predisposing Genes for Colon Cancer: Controlling Destiny

Your lifestyle can influence the kinds of diseases you get. Exercise and a healthy diet can help prevent many forms of cancer.

Meet Carlos. Architect, age 45, father of three children. His 53-year-old brother recently died of colon cancer, at the same age their mother died from the same cancer. Colon cancer is the country's second leading cause of cancer death after lung cancer, affecting one out of 200 people. Carlos learned that his brother's form of cancer *(familial adenomatous polyposis)* is associated with two genes and is inherited through families.

The doctor said there was good news for families like Carlos': there is now a test for the genes. She offered to give this test to Carlos and his children.

Carlos hesitated. He did not know if he wanted to find out if he would get cancer like his brother. The doctor explained that these genes do not give cancer, but rather they give the predisposition to develop cancer. That is, people with them have a high risk of developing cancer, but it is not definite in the way that people with the Huntington's gene will definitely get HD.



Furthermore, people can reduce their risk of getting colon cancer. They can eat a low-fat, high-fiber diet, exercise, and avoid alcohol and tobacco. They can have regular medical exams to see if precancerous growths are beginning to form. If they are, these growths can be removed before cancer develops. Finally, if cancer does develop, it can be treated before it spreads and becomes incurable.

Carlos wondered whether his children were too young to have a test for a disease that will not affect them until their adult years. The doctor explained that the cancer itself may not form until later, but the precancerous growths often begin in the teens, and good diet and exercise habits should begin early. (See next page.)■

The HGP and Model Organisms

The discoveries of two genes for colon cancer were possible because of research on "model" organisms – that is, other species. Researchers first found genes in yeast and bacteria that help repair copying mistakes made during DNA duplication. These genes work like a spell checker, finding and correcting "typos." Using public databases, the researchers found matches to these genes in the human genome. They then learned that when these human "spell checker" genes are faulty, mistakes can build up and lead to colon cancer. This research is just one example of how studying other organisms is a short cut to learning about human genes and disease.▼

what if?

What if Carlos' brother had insisted on the right to privacy and had not wanted Carlos to know that his cancer was hereditary?

What if the cost of the tests and the concern about health insurance keeps Carlos from getting the care that could save his life?

A QUESTION OF ETHICS

Privacy and Medical Records

Carlos spoke to a genetic counselor about the privacy of the test results. He had heard that health insurers can see medical records and that some companies might not insure people with serious medical conditions. The counselor explained that Carlos might be able to keep the result confidential if he pays the $1,000 fee for the test himself. If the insurance company pays, it has access to the records. She gave him information about "Genetic Privacy" acts that have been introduced into several state legislatures and the U.S. Senate, but cautioned that no one knows yet what the outcome of this legislation would be.

Other Headliner Genes

Scientists are now discovering more and more genes that affect large numbers of people. They include genes linked to breast cancer, skin cancer, heart defects, Alzheimer's disease, and baldness. Other genes are linked to behavioral traits like alcoholism, impulsiveness, and mental illnesses. We do not yet know how society will treat people who have these types of genes.

Pick a recently discovered gene and research it. Is it a predisposing gene? Is it dominant or recessive? Which chromosome is it on? What protein does it make or fail to make? How will this discovery help develop a treatment?

What if you knew you had a gene for skin cancer or alcoholism? Might you be able to decrease your chance of getting skin cancer or becoming an alcoholic?

What if you sunbathed a lot or drank alcohol anyway? Would you be personally responsible for your skin cancer or alcoholism? Would you be able to "blame your genes" ?

Role Play Activity

Pretend you are one of the people below. Prepare to dramatize your role for the class as your teacher will explain. (Teachers: see suggestions in the Teacher's Guide.)

Carlos or Carla: Will you go for the genetic test? If the test is positive, who will you tell? What will you do?

15-year-old child: Do you want to get tested? If you have the predisposing genes, would you substitute fresh fruit and vegetables for junk food now, just to avoid cancer when you're 40 or 50? Would you have yearly exams?

Genetic counselor: Should Carlos pay for the tests himself? What would you advise his children to do – get tested or wait? Until what age?

Doctor: What should Carlos and his children do? Do you need the results in their medical records in order to plan better treatment?

Employer: Would you promote Carlos to a high-level, responsible position if you knew he had a colon cancer gene? Would you keep him in your company's health insurance plan? (What deadly genes might you have that have not yet been discovered?)

Health Insurer: If Carlos and his children have a high risk for cancer, will you deny them insurance because of the high cost of treatment? Should you maintain coverage but raise their rates? Should you pay for preventative measures, such as nutritional counseling or yearly exams, in hopes of avoiding paying for cancer treatments later?

The Obesity Gene

The mouse on the left has a defective gene that causes obesity. Researchers have found a human relative of this gene.

Jeffrey M. Friedman.

If you worry about your weight, you're not alone. About one out of three Americans weighs more than 20% over their ideal weight. We don't exercise enough, and we eat too much of the wrong kinds of food. Obesity is not just an adult problem. American children are getting fatter every year, too. We pay for our paunches with our health: obesity increases our risk of heart attack, diabetes, cancer, high cholesterol, and early death. Even though we spend $30 billion a year to lose weight, most of us don't succeed.

Now, thanks to the *Human Genome Project's* study of other organisms, we understand one reason why it's so hard to diet. We're designed for the "caveman" days when food was hard to find and we had to gorge whenever food was available. The genes that gave our bodies that craving for food helped us survive. We still have those same genes, even though we now have supermarkets and fast food joints.

A group of researchers found one of those genes while studying obese mice. They entered the sequence for this obesity gene into a public database and, voilà!, they found a related human gene. This gene produces a protein called *leptin* in the body's fat cells. When there is a lot of leptin, the brain thinks you have enough food and tells you to stop eating. When the fat cells shrink and there is less leptin, the brain tells you to find food.

When the obesity gene malfunctions, it does not make enough leptin. The brain thinks you are starving even if you have plenty to eat.

When people heard about this next report, they almost leapt for joy: when mice are given leptin, they lose a lot of weight. Would a daily dose of leptin work the same in human bodies?

Unfortunately, there's no simple way to a perfect body. Overweight humans do not always have low leptin levels. The problem with humans is not a shortage of leptin, but rather an inability of the brain to receive signals from the leptin. The body may be yelling "stop eating," but the brain simply does not hear.

In addition, there are other genes involved in obesity that we are starting to discover. Furthermore, genes are not the only thing controlling our eating habits! Regardless of the final answer, discovering the obesity gene in mice is helping scientists learn a lot more about people.■

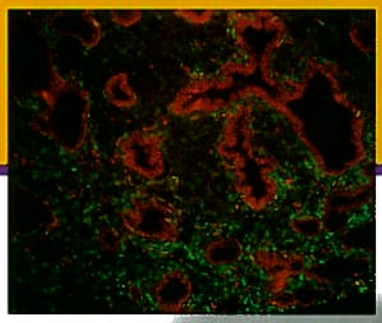
A QUESTION OF ETHICS

Your Genome is No Crystal Ball

Advances in genetics may give us a map of our genes but they will not give us a map to our future. The interaction of each person's unique combination of genes with each other and with the environment will always produce unpredictable results. In addition, people make choices about how to behave. According to one researcher, interpreting an individual's genetic map is more like predicting the weather than fortunetelling. Weather depends on many probabilities, variations, and environmental conditions – except it doesn't make choices about whether to rain or shine!

Who Gets the Treatment?

If a genetic treatment could treat obesity, who should take it? Just people with medical problems? People who want to lose five pounds? Should people be forced to become thin if their weight gives them medical risks? How would you feel about taking the treatment? Would you tell your friends and family, or would you want to keep it secret?



Heinz-Ulrich Weier, Lawrence Berkeley National Laboratory

An early pay-off of the Human Genome Project and its new technologies: "Chromosome painting" images allow researchers to study genetic changes that signal cancer and other diseases.

John Bigelow Taylor, from The Olmec World, Princeton/Abrams, 1995

This clay figure comes from the Olmec culture of Mexico (1200-900 B.C.) The Olmec people probably thought this woman was beautiful.

What inherited traits (eye color, hair color, shape of nose, etc.) can you see in your family? Which are from your mother's side? Your father's? Do you share other traits with family members, such as an interest in math, a talent for music, or tendency to be disorganized? Do you think these similarities have a genetic basis? Are they learned by example? Or are they a mix of "genes" and the "environment"? Which of your characteristics do you think are not under genetic control?

Beauty is Relative

Our society thinks thin is beautiful. But in other cultures and other times, thinness was a sign of poverty. Well-to-do people liked to look "well fed" and women with large hips were admired, perhaps because they were considered very fertile. Such values are reflected in the art and crafts of these cultures.▼

Key to Cover

1) **A model of DNA, the universal code for life.**
2) **An eye, often used as an example when explaining inheritance.**
3) **Students: future scientists or people providing DNA samples.**
4) **Autoradiograms, used to analyze DNA segments.**
5) **A 96-well plate, used to analyze cells and to clone cells.**

REFERENCES

DOE Human Genome Program
Department of Energy
19901 Germantown Rd. ER-72 19901
Germantown, MD 20874

http://www.er.doe.gov/production/oher/hug_top.html

Human Genome Management Information System (HGMIS)
Oak Ridge National Laboratory
1060 Commerce Park, MS 6480
Oak Ridge, TN 37830

http://www.ornl.gov/hgmis

Publications available on line: *Human Genome News* and *DOE Primer on Molecular Genetics*.

NIH National Center for Human Genome Research (NCHGR)
Building 31, Room 4B 09
31 Center Drive
Bethesda, MD 20892

http://www.nchgr.nih.gov

World Wide Web Addresses for Genomic Data Bases

GenBank:
http://www.ncbi.nlm.nih.gov/

Genome Sequence Data Base:
http://www.ncgr.org

Genome Database:
http://gdbwww.gdb.org/

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http://www.bio.com/pba

Dear Students:

We are pleased to provide you with this expanded national issue of *Your World/Our World,* which addresses the science and applications of the *Human Genome Project*. *Your World/Our World* presents information on the exploration of the frontiers of modern biotechnology in a way we hope you find interesting. Each issue presents recent scientific advances and their impact on society in a particular field of biotechnology. We place special emphasis on career opportunities by highlighting the contributions of women and men of different races and national origins.

This issue represents our first national distribution and our first twenty-four page issue. We hope you enjoy it.

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1. During your lifetime there will be tremendous discoveries in this field, and you'll want to understand what those discoveries mean for you, your friends, and your family.

2. You can help make these discoveries if you continue studying science and math.

We hope you join us in discovering the promise of biotechnology for your world and our world. *Your World /Our World* is produced twice each year, and is available in classroom or individual subscriptions. We welcome your comments and suggestions.

Sincerely,

Jeff Davidson
Executive Director
Pennsylvania Biotechnology Association & Alliance for Science Education

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