CHAPTER 4

Controlling Our Genetic Futures

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Chapter 4 Overview

INFORMATION COMING FROM genetic laboratories around the world. presents us with an ever-growing the list of potential actions in the area of human genetics that have become technically feasible. But it provides few guidelines for deciding which of those actions would be ethically desirable.

History provides us with unambiguous evidence that not all actions that might be undertaken because someone thinks that they would improve the human gene pool are ethically acceptable. The first era in which it was widely believed that genetics could be used to produce great benefits for humanity was the eugenics era (~1870-1945). In the United States, the eugenics movement led to blatant racism, open class hostility, and the forced sterilization of hundreds of thousands of underprivileged individuals who were judged (by those in positions of privilege and power) to possess inferior genes. In Germany the eugenics movement ultimately led to the horrors of the holocaust.

Nothing vaguely resembling this is being proposed today. Nevertheless, certain of the things that are becoming possible in the sphere of human genetics do raise serious questions.

Some of the questions raised by the new genetics are highly personal, such as: How much do I want to know about my own genetic constitution and that of my prospective children? Others are economic, such as: Would screening all people of child-bearing age to identify cystic fibrosis carriers cost society more or less than is presently spent to care for children with cystic fibrosis? But the most vexing issues, and thus the ones most deserving of thoughtful, widespread discussion, are ethical ones, such as: How much responsibility do members of the present generation have to promote the genetic well-being of their descendants? To what lengths should prospective parents be expected to go to prevent giving birth to a child with a serious heritable disease? If and when it becomes possible, should parents be permitted to have their germ cells modified genetically, in order to produce "designer babies" with improved physical appearance, athletic ability and/or intelligence?

Ethical considerations are often excluded entirely from the science curriculum because they are considered too controversial. But if ethical issues arising from human genetic studies can not be discussed in a calm and rational manner in a biology classroom in which human genetics is being studied, where are they likely to be discussed that way?

Although a strong case can be made for introducing students who are studying genetics to some of the associated ethical issues, it does not follow that the more controversial an issue is, the more productive a classroom discussion of it would be. Therefore, this chapter does not go out of its way to introduce some of the most vexing and divisive questions raised by the modern genetics (such as the "designer baby" issue mentioned above). Rather, it uses the case-study method to engage them in discussing some more benign ethical issues that are raised by recent advances in genetic testing.

The first two case studies are presented in a video tape entitled Promise & Perils of Biotechnology: Genetic Testing. Each of the young women featured in this tape asked to be tested, so that she cold learn whether she had inherited a serious disease that affected one of her parents. Both women tested positive for the disease in question, but the implications of their results were very different, because of the differences between the two diseases with respect to.

The next section of the chapter first introduces some of the basic features of value-based deliberation and decision making, and raises some of the problems and issues raised by genetic testing. The essence of this section is summed up in the following excerpt: "Experience indicates that it is next to impossible for individuals who come from different religious and cultural backgrounds to agree on an appropriate course of action in a difficult situation if all of them merely shout out opinions that are based on their own religious doctrines or 'gut feelings.' On the other hand, agreement is more likely to be achieved if all members of the group try to evaluate calmly how each possible alternative course of action would relate to certain human values that they agree in advance are really important…." The students are then given a list of such values, and challenged to work cooperatively to decide how the list might need to be modified to reflect a set of values that they can all agree are really important.

Having been thus introduced to the conceptual framework of value-based group decision making, they are presented with two rather different scenarios involving genetic testing, and asked to evaluate them within an ethical framework.

The chapter concludes with a set of options that you might consider for exploiting the "DNA in the News" articles that your students have been collecting, in order to generate a "capstone experience" for their study of genetics.

FOR MORE INFORMATION

Up-to-the-minute news stories relating to the Human Genome Project and other aspects of genetics are regularly available at http://www.ornl.gov/hgmis/archive/headlines.html. Human Genome Project educational materials for teachers are available at http://www.ornl.gov/hgmis/education/education.html.

CHAPTER 4

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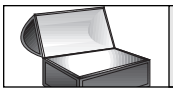
SECTION A

Biotechnology: Panacea or Pandora's Box?

Chapter 4: Section A Background

THIS OPENING SECTION of Chapter 4 uses a video tape to introduce two rather different real-life case studies involving genetic testing, and then asks your students to indicate whether they think they would have made the same choices about being tested as the two women in the video did.



A.1

Promise & Perils of Biotechnology: Genetic Testing

(A Video Presentation) STUDENT PAGE 212

LESSON OVERVIEW

This video tape (which was made by and for teachers) will introduce your students to two young women, both of whom are from families with a history of serious genetic disease, and both of whom sought to learn whether they had inherited the disease alleles in question.

Jennifer Jones sought to find out if she had inherited the allele for Huntington's disease (HD) from her father. She knows that if she learns she has the HD allele there is nothing she will be able do to avoid developing this devastating disease at some time in the future. Yet she insists on knowing, because she is considering marriage and raising a family, and does not want to risk passing on the HD allele to a child. When she learns that she does have the HD gene, and therefore is doomed to develop HD later in life, she resolves to cherish each day that she is alive and well, for as long as she can.

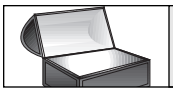
The second case involves Lily Ann Shofer, who had been tested to determine whether she inherited her father's mutant gene that causes dangerously high blood cholesterol levels, which then lead to coronary artery disease and premature heart attacks. Lily Ann learned not only that she had inherited this allele, but that her daughter Lora had also. In contrast to Jennifer, however, Lily Ann and Lora are not left without a way to fight back. By changing their life styles they are able to greatly reduce their blood cholesterol levels and thereby reduce their risk of suffering coronary artery disease and heart attacks.

TIMELINE

This tape runs about 25 minutes.

ADVANCE PREPARATION

Promise & Perils of Biotechnology: Genetic Testing is available from Cold Spring Harbor Laboratory Press (Tel. 1-800-843-4388; www.cshl.org/books/videos/prom-per.htm).



A.2

Worksheet for

Promise & Perils of Biotechnology: Genetic Testing

STUDENT PAGES 213-214

TIMELINE

It should take about 5 minutes to answer the first three questions before the tape is shown, and about 10 minutes to answer the last six after the tape has been shown.

Before viewing the video, answer the following three questions:

1. What does genetic testing usually involve?
   Isolating DNA from white blood cells, using the polymerase chain reaction to amplify the gene in question and then using gel electrophoresis to determine whether the wild-type or mutant allele are present.

2. Who needs genetic testing?
   Anyone whose family is known to have a history of a genetic disease, and who wants to know if they are similarly afflicted.

3. What are some of the reasons for and against undergoing a genetic test?
   For: you will learn whether you are likely to develop a disease that runs in the family, and/or are likely to pass it on to your children.
   Against: you may learn that you will suffer later on from a serious disease that cannot be prevented or cured.

After viewing the video, answer the remaining questions:

4. Now that you have seen the video, would you answer any of the above questions differently? Explain.
   Answers will vary.

5. If you had been in the same situation that Jennifer Jones was in, would you have wanted to be tested as she was? ___ Why or why not?
   Again, answers will vary. Some students will probably say that they would want to be tested for the same reasons that Jennifer did, others will probably say that they would not want to know that they were going to suffer from HD.

6. If you had taken the test and learned that you had the gene for Huntington's disease, how would you have used the information?
   Answers here will likely vary even more.

7. If you had been in the same situation that Lily Ann Sholer was, would you have wanted to be tested as she was? ___ Why or why not?
   Most students would be expected to answer "yes" in this case, because if you have this particular gene, you have everything to gain, and nothing to lose by knowing about it.

8. If you had been in the same situation that Lily Ann Sholer was, would you have wanted your daughter to be tested also? ___ Why or why not?
   Again, most students would be expected to answer "yes," for the same reason.

9. Is there anything that you think Lily Ann and her daughter should do in addition to eating a low-fat, high-fiber diet and taking their medicine in order to lower their chances of having a heart attack?
   Get lots of exercise every day and try to avoid stress.

10. Do you think it is fair that Lily Ann can not get insurance for Lora because of Lora's genetic condition? Explain:
    Answers will vary, but this question touches on one of the issues that many people are most concerned about: whether insurance companies should be able to find out about a person's genetic constitution and use this information to deny or cancel insurance coverage. See below.

FOLLOW UP

After the students have finished filling out their worksheets, you might want to take the rest of the period to discuss their reactions to the tape, and to ask what questions it raised that they did not think were adequately addressed.

The question of insurance coverage is one potentially interesting topic for further discussion. Is it fair that people with a genetic condition like Lora's cannot get insurance if they have adopted a life style that minimizes their disease risk? On the other hand, would it be fair to allow people who know that they have a gene that makes them likely to develop a very serious and expensive disease to hide this fact from their insurance company? As we enter an era in which more and more people will be tested for more and more genetic conditions, how should society deal with this issue? Would a governmental policy ensuring universal health insurance contribute significantly to the solution of such problems?

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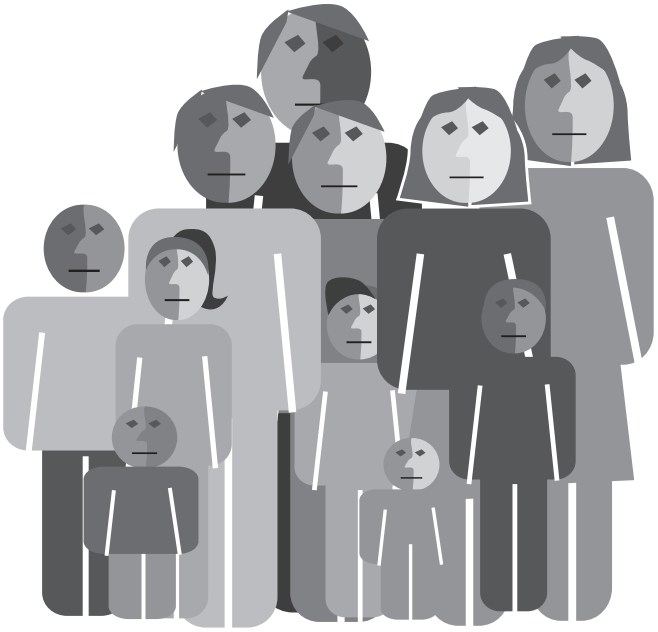

SECTION B

Resolving Genetic Testing Issues: An Introduction to Group Decision Making

Chapter 4: Section B Background

From the beginning of the Human Genome Project (HGP), part of its funds have been set aside every year to support the Program on Ethical, Legal and Social Implications of the Human Genome Project (the ELSI Program, for short). This reflects an advance understanding by scientists and legislators that an active and sustained effort would be required to assure that the genetic information being accumulating at public expense in the HGP would be used to promote public good. Thus, ELSI supports a diverse set of studies and conferences involving specialists in bioethics, clinical medicine, law and other specialties to subject actual or proposed developments in human genetics, gene therapy, and so forth to regular and detailed scrutiny. But experts can do only so much. The ELSI Program supports research that defines the issues and outlines policy options with respect to human genetics; but neither it nor its grantees have the authority to make any sweeping policy decisions. That is the task of that faceless mass known as "the public." Assuring that our new genetic technology will be used in ways that are not only wise, humane, and effective, but are also deemed socially acceptable, will require the involvement and cooperation of public citizens that are both genetically literate and capable of calm, non-confrontational group deliberation.

This is where you, as a biology teacher, come into the picture.

Nothing is gained, and much is lost, of course, if what was intended to be a classroom discussion of a moderately controversial issue degenerates into a shouting match in which students hurl slogans and epithets at one another. However, this sort of confrontational approach to dealing with controversy is probably the approach that many students will have seen most frequently on TV news and talk shows. Forestalling such a counterproductive confrontation will require establishing a different kind of model in advance.

This section of Chapter 4 is directed to that end.

A great deal of information about ELSI activities, programs and publications is available at http://www.nhgri.nih.gov/About_NHGRI/Der/Elsi.html.

B.1

A Value-Based Approach to Group Decision-Making

STUDENT PAGES 216-222

LESSON OVERVIEW

The purpose of this section is to provide the students with a process that they should be able to adapt for organizing a non-confrontational discussion of any potentially controversial issue, not just the particular issues raised in this chapter. Undoubtedly many members of your class will be completely unfamiliar with this kind of value-based approach to discussing difficult issues. Thus, they will need help learning to use it, just as they needed help learning to use a micropipettor.

The critical first step in developing a value-based approach to group decision making is agreeing upon a set of values that all members of the group agree are important, independent of any particular case that is about to be considered. Therefore, after the students have had a chance to read and think about this selection (preferably as homework; see below) you should probably plan to lead a classroom discussion regarding how the list of values given in this section should be modified in order to serve as a common starting place for consideration of some of the issues raised by genetic testing.

TIMELINE

It would probably work best to assign both B.1 and B.2 as homework, and ask the students to come to class with their own written suggestions for how the list of values given in B.1 should be modified. Then it should probably be possible to discuss all of the values on this list and resolve any differences of opinion students have about modifying the list in about 20 minutes. This will probably go best if you act as moderator for the discussion, try to ameliorate strong differences of opinion, and write items on the board as the class comes to agreement about them.

B.2

New Genetic Tests Lead to Difficult New Questions

STUDENT PAGES 223-224

LESSON OVERVIEW

The purpose of this reading assignment is two-fold: (1) To alert your students to some of the difficult questions that our society will need to address in the near future as a result of our rapidly increasing ability to detect genetic diseases. (2) To make the point that these issues have the potential to intensify divisions within our society unless we learn to discuss them in a thoughtful and non-confrontational manner.

TIMELINE

It should not take an average student more than about 6-8 minutes to read this unit. It would probably work best, however, to assign both B.1 and B.2 as homework.

CHAPTER 4

Controlling Our Genetic Futures

SECTION C

Genetic Testing: Two Case Studies

Chapter 4: Section C Background

PERHAPS THE MOST WIDESPREAD misconception about human genetics is that individuals who suffer from serious genetic diseases differ from the rest of us who are healthy because they have "bad genes" and we have "good genes." All of us – sick and well alike – have a combination of "good" and "bad" genes (or, more properly, normal and mutant alleles). On average, each of us has about twenty mutant alleles that could cause us to have a heritable disease at some time, or under some conditions, or to pass a heritable disease on to one or more of our children. Those who suffer from a serious heritable disease generally differ from the rest of us not because they have more "bad genes," but because they have had bad luck in the genetic lottery, and have inherited an unfortunate combination of mutant alleles. But even such very sick individuals generally have normal, "healthy" alleles at more than 99.99% of all their genetic loci.

Nothing in the area of human genetics raises more hopes or greater fears than genetic testing. The purpose of genetic testing is to identify which of us may have some particular, potentially worrisome mutant allele hidden among all of their normal alleles, so that they can take steps to minimize unnecessary suffering in themselves and their offspring. In the past, two major efforts were made to do this on a large scale, by screening many individuals within particular ethnic communities for particular mutant alleles that were known to be prevalent in those populations. The contrasts between these two screening programs are instructive.

THE DIFFERENCES IN APPROACH AND OUTCOME OF TWO LARGE-SCALE GENETIC SCREENING PROGRAMS

The history of Tay-Sachs disease in the United States since 1970 illustrates the fact that when genetic screening is done right it has the potential to play an enormously positive role in the life of an entire community.

Tay-Sachs is an autosomal recessive disease. Homozygous Tay-Sachs babies appear healthy for about the first six months, but then they lose motor skills they had begun to develop, become deaf, blind, paralyzed and totally helpless, and almost always die by age three. Although the molecular nature of the disease has been known for decades now,* there is still no way to slow the progress of the disease, let alone cure it.

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* Tay-Sachs is a result of a mutation in the gene that encodes an enzyme called hexosaminidase A. Hexosaminidase A normally functions in the brain to destroy excess quantities of a particular type of lipid molecules, called gangliosides. Gangliosides are essential brain components that are necessary for proper transmission of nerve impulses. Nevertheless, if they are allowed to accumulate to excessive levels (as they do in the absence of hexosaminidase A) they drastically interfere with brain function.

It is believed that one reason that the Tay-Sachs allele became so abundant in the Ashkenazic population is that heterozygotes are resistant to tuberculosis. Thus, when tuberculosis swept though the ghettos of eastern Europe, as it did frequently during the middle ages, Tay-Sachs carriers had a survival advantage over those who lacked the Tay-Sachs allele.

Tay-Sachs is extremely uncommon in most human populations. However, as one consequence of hundreds of years of inbreeding, the frequency of the Tay-Sachs allele is unusually abundant among people of Ashkenazy Jews (people of eastern European Jewish ancestry).** About 1 in 30 adults in this population is a Tay-Sachs carrier, and historically about 1 in every 3,600 Ashkenazy babies has suffered from the disease.

When a test that would detect Tay-Sachs carriers became available in the early 1970s, a community-based voluntary screening program was initiated in the Washington-Baltimore area by a committee of leading rabbis, physicians, and concerned lay people. When the program began only 2% of the people in the community had any idea what the words Tay-Sachs referred to; but a year later 95% did, and thousands of people had been tested voluntarily. Word spread quickly, and soon testing programs were set up, and hundreds of thousands were tested, in communities around the US and five other countries in which there were sizable populations of Ashkenazim. Although most such community-wide Tay-Sachs screening programs have long since ended, many rabbis continue to include advice about Tay-Sachs screening in their premarital counseling. As a result, by now fewer than 10 children with Tay-Sachs are born in the US each year. Beyond doubt, this screening program has protected thousands of households from experiencing the agony of this dread scourge.

If the Tay-Sachs screening story provides a model at the positive end of the spectrum, however, the sickle-cell screening program provides a model at the other end of the spectrum.

Sickle cell anemia is an autosomal recessive disease in which a mutant hemoglobin molecule (HbS) causes red blood cells (RBCs) to become seriously deformed (sickle-shaped) when they are depleted of oxygen. Sickled RBCs pile up in capillaries like logs in a log jam, and block blood flow. The resulting lack of adequate oxygen in the tissues causes extreme pain, particularly in joints and other sensitive body regions. Such episodes can last from hours to weeks at a time, and cause extensive secondary tissue damage. About 1 person in 10 in the African-American community is a carrier of the HbS mutation, and about 1 person in 400 is a homozygote afflicted with sickle-cell disease. Under nearly all conditions, carriers (although they are sometimes said to have “sickle-cell trait”) are completely symptom-free.

A sickle-cell screening program was initiated at about the same time as the Tay-Sachs screening program. But in contrast to that program, it was an unmitigated disaster, for several reasons: (1) The sickle-cell screening program was initiated and operated from outside the black community, rather than from within. (2) It never included the kind of effective community-based public-education or counseling effort that accompanied the Tay-Sachs program. (3) Whereas Tay-Sachs screening was always voluntary, in several states sickle-cell screening of African-American children was made mandatory, even though the only valid scientific objective of such screening was to discourage carriers from child-bearing, since there was no significant treatment available for those with the disease. (4) Although

** French Canadians (including their Cajun descendants in southern Louisiana) constitute a second population in which the Tay-Sachs allele has become unusually abundant as a result of extensive interbreeding.

the program was begun by people with good intentions, before long many people both inside and outside the black community who had ulterior motives got involved in promoting sickle-cell screening for their own political purposes. (5) Test results often were not treated with appropriate confidentiality.

Among the consequences that followed from this totally misguided program were the following: Children with the disease were stigmatized. Carriers, (who almost never had the significance of their carrier status adequately explained to them) regularly suffered acute and unreasonable loss of self esteem, and in some cases were ostracized. Insurance companies raised premiums for all known carriers. Many corporations initiated their own mandatory screening programs for black employees, and then discriminated in various ways against the carriers they discovered. For example, all major airlines grounded or fired employees found to be carriers. Similarly, the US Air Force Academy refused admission to all applicants who were carriers – until this policy was rescinded by court decree six years later. Finally, and most importantly, the whole episode intensified feelings within the black community that the white medical community was not to be trusted, and would always be more likely to use new medical knowledge to increase discriminatory treatment of the black community than to help it. This attitude has persisted, and has had profound negative consequences more recently with respect to efforts to enlist members of the black community in programs of AIDS education, prevention and therapy.

MORE RECENT GENETIC SCREENING ACTIVITIES

Given that grim bit of history, it is not surprising that whenever the topic of genetic screening comes up, most private individuals express concerns regarding three main issues: (a) confidentiality of results, (b) possible insurance discrimination, and (c) possible employment discrimination. Such concerns were among the many reasons that a more recent population-screening program for cystic fibrosis did not generate much interest on the part of either physicians or the public, and was discontinued.

Cystic fibrosis (CF) is an autosomal recessive disease that is the result of mutations in the gene encoding a transmembrane chloride transporter protein (see Chapter 1 Section E Background for details). It is the most prevalent genetic disease among those of white European ancestry. In that population, the carrier frequency is about 1 in 23, and nearly 1 child in 2,000 is homozygous, and thus has CF.

In the early 1990s, not long after the CF gene had been identified and a carrier test became available, the ELSI program of the NIH (see Background to Section 4.B) sponsored a number of trial screening programs around the country. However, in study after study the vast majority of people (in one study many more than 99%) failed to take advantage of an offer of free carrier testing. In one study, nearly 25% of those offered a test while they were already in a clinic accepted the opportunity – but only if they were told they did not have to do anything else. The acceptance rate dropped to 4% when patients were told that in order to be tested they would have to attend a short educational session! Even most siblings of CF patients declined the opportunity to be tested. Acceptance rates were highest among individuals who were about to start a family or were pregnant for the first time, but couples who already had children had much less interest in being tested.

In light of all such studies, a panel of experts convened by NIH in 1997 issued a statement that said: "Genetic testing for CF should be offered to adults with a positive family history of CF, to partners of people with CF, to couples currently planning a pregnancy, and to couples seeking prenatal care. The panel does not recommend offering CF genetic testing to the general population or to newborn infants…."

Because CF had seemed like the best candidate for a new wide-scale screening program in the early 1990s, and it failed, most experts now think that it is unlikely that any more wide-scale screening programs to identify carriers for one particular disease will be undertaken in the foreseeable future.

At the present time, therefore, genetic screening is being performed almost exclusively on a case-by-case basis, for individuals whose ethnic background and/or family history suggests the possibility that they might have a particular heritable-disease allele. As the two case studies presented in this chapter will reveal, when such testing reveals that a family member has such an allele, there are often some difficult personal, ethical issues raised in addition to the more generalized ones that were discussed above.

However, events just over the horizon may soon blur the distinction between individual and group genetic screening activities.

A DRAMATIC CHANGE IN GENETIC TESTING METHODS MAY LIE JUST AHEAD

Over recent years there has been a steady increase in the number of disease-causing genes that can be detected with conventional molecular methods. Nevertheless, the number of such tests is still extremely small, relative to the total number of diseases that are known to have strong genetic components, and it is still difficult and time-consuming to identify each such allele in the conventional gene-by-gene manner.

However, two technical developments that have grown out of the Human Genome Project hold the potential to change that situation dramatically, and to provide a way of rapidly identifying mutations associated with hundreds of different diseases, as well as countless other aspects of the phenotype. These revolutionary new developments bring together a set of clever analytical devices known as DNA chips, and a set of genetic elements known as single-nucleotide polymorphisms, which will now be described sequentially.

DNA chips are molecular analogs of computer chips. But instead of holding a set of electronic circuits on a tiny surface as a computer chip does, a DNA chip holds a defined array of single-stranded DNA molecules of known sequences at defined spots on a microscope slide. Such slides are made by a computer-driven robot that applies different kinds of DNA molecules to each of many tiny spots on the slide, in a very precise rectilinear array (see Figure A). One such robot is able to place 150,000 different DNA samples on a single microscope slide, and to make hundreds of identical DNA chips that have each particular kind of DNA in the equivalent position on every chip.

Because all of the DNA molecules in any given spot on a chip are identical in sequence and single stranded, each spot serves as a potential binding site for one unique kind of DNA that is complementary in sequence to the DNA present in that spot. Thus, a chip with 150,000 different DNA spots can serve as a device for determining – in one rapid procedure – which of 150,000 slightly different DNA molecules are present in a particular DNA sample!† If necessary, many chips carrying different DNA molecules can be used in parallel, so there is no limit to the number of different DNA sequences that can be analyzed with such chips.

The way a DNA chip is used to analyze a sample is as follows: First the DNA molecules in the sample to be analyzed are coupled covalently to a dye that makes them fluorescent. Then the solution of fluorescent DNA is spread over the surface of the DNA chip and incubated under conditions that permit molecules in the solution to find complementary molecules on the slide and hybridize to them (that is, form base-paired double helices with them). Then the chip is washed to remove all unbound DNA molecules. At this point the chip is ready to be examined, but the spots on it are too tiny to be resolved with the naked eye. They can only be evaluated with a fluorescence microscope, which is a microscope that allows one to illuminate a specimen with light of the wavelength that will excite the dye molecules, while viewing the longer wavelength light that is emitted by the excited dye molecules. When the chip is viewed in such a microscope, it will be seen that some spots are brightly fluorescent and others are dark. The former will be spots for which complementary DNA molecules were present in the test sample, and the latter will be ones for which complementary molecules were not present.

However, no human would have the patience to evaluate and record results for all 150,000 spots on a single DNA chip, let alone a pair of chips that were being used to compare two different DNA samples, A and B. But this is precisely the kind of mindless task that computers are good at. So the computer drives a pair of motors that move the chip past the microscope lens step by step, so that every spot can be evaluated in some standard sequence. Each spot is scored by the computer as a 1 (bright) or 0 (dark), and the results are stored in its memory banks. A simple program will then generate a printout indicating which DNA sequences were present in sample A but not B, in B but not A, in both A and B, and in neither A nor B. More complicated programs could compare a much larger set of DNA samples, of course, and pick out more complex patterns within the population tested.

So what kinds of DNA will be bound to such chips, and what kind of information will then be generated about two or more DNA samples? Enter SNPs!

Single-nucleotide polymorphisms, or SNPs (pronounced "snips"), provide an exceptionally powerful new approach to human genetics. The term polymorphism refers to any genetic trait that exists in two or more alternative forms within a population, and that thus distinguishes members of a single population. (For example, leopards exhibit a coat-color polymorphism: some leopards are solid black, but most are tan with black spots.) SNPs are

†Actually, DNA chips can be used to analyze either RNA or DNA samples, but only their use in DNA analysis is relevant to the present discussion.

polymorphisms at the DNA level that involve alternative nucleotides at only location within a stretch of DNA sequence. For example, the following three sequences might be found with different frequencies in different human genomes:

...CGGTAT**G**CGTTACGG... (most abundant)
...CGGTAT**A**CGTTACGG... (less common)
...CGGTAT**C**CGTTACGG... (very rare)

The DNA chips that will soon revolutionize human genetics will be **SNP chips** that have will SNP DNAs on each spot (often with two alternative versions of the same sequence on adjacent spots; see Fig. A).

Some SNPs were identified years ago via the slow, difficult, pre-1990 process of cloning and sequencing two different alleles of a known gene. For example, it was established more than 30 years ago that sickle cell anemia is the result of a SNP in the gene encoding the _-globin part of the hemoglobin molecule: where a section of the normal _-globin gene reads …TGTGGGC**T**TCTCTTTAGT…, the equivalent DNA region in individuals with sickle cell anemia reads …TGTGGGC**A**TCTCTTTAGT. Other SNPs have been discovered in the Human Genome Project. However, several simpler, faster ways are now being used to find new SNPs by the hundreds of thousands. For example, a chip can be prepared with thousands of pairs of synthetic DNA molecules that differ at only a single nucleotide position. The computer then picks out all those pairs in which one spot lights up with some human DNA samples and its partner lights up with others.

Most SNPs that are identified in this kind of arbitrary manner will convey very little information by themselves. But when DNA samples are analyzed with respect to thousands or millions of such SNPs at once, it is virtually certain that each individual will have a SNP profile that that is more distinctive than his or her fingerprints are. Furthermore, when many such profiles have been stored in a data bank, a computer will be able to pick out certain combinations of SNPs that are strongly correlated with most any phenotypic trait that can be defined – such as bright red hair, or a predisposition to coronary artery disease, or…you name it!

Pharmaceutical companies, working individually and in an international "SNP Consortium" are engaged in a massive effort to identify millions of SNPs and develop SNP chip technology. By early 2001 they had already identified more than one and a half million human SNPs that were present in more than 1% of all individuals tested!

Why are the drug companies so interested in SNP chips? There are two major reasons.

One of the major problems drug companies struggle with are individual differences in response to drugs. People can differ by as much as 25-fold in their sensitivities to certain drugs, such that a drug dosage that is safe and effective for most people may have no effect at all in other individuals, but may cause serious damage in – or even kill –others.

Most such differences in sensitivity are believed to be heritable.†† And many of them are drug-specific. That is, persons who suffer severe side effects from one drug may get nothing but relief from another drug that is sometimes used to treat the same condition.

Pharmaceutical executives believe that if they could identify people with these heritable differences in drug sensitivity, they could:

- Improve their drug development strategies.
- Design and perform more rational clinical trials of new drugs.
- Provide physicians with guidelines for determining which patients are most likely to gain the benefits or suffer the adverse side effects of any particular medication.

The second reason for intense interest in SNP chips is that they might permit drug companies to engage to a greater extent in preventive (as opposed to therapeutic) medicine. If sufficient numbers of SNP profiles and medical histories were available in central data banks, it might become possible for computers to recognize combinations of SNPs that identify individuals with the strongest hereditary predisposition to develop certain multifactorial diseases, such as diabetes, heart disease, or cancer. This could greatly improve clinical trials for testing agents that are designed to prevent, rather than treat, one or another of these diseases.

The time may not be far off when a person visiting a physician for the first time may be asked to permit a blood sample to be used for establishment of a SNP profile. Having such a profile on record might profoundly improve the physician's ability to diagnose, treat, predict, and prevent medical problems.

But at the same time, SNP-chip testing will inevitably raise – more strongly than ever – questions regarding confidentiality, potential insurance discrimination, and potential employment discrimination.

†† Such differences in sensitivity can be caused by heritable differences in the proteins involved in absorbing a drug from the digestive tract, transporting it through the body, modifying it chemically in the liver, binding it to the surface of, or transporting it into, the cells where it is supposed to have an effect, or excreting it in the urine.

Roger Patton's Dilemma STUDENT PAGES 226-228

LESSON OVERVIEW

Your students are asked to put themselves in Roger Patton's shoes and try to decide what he should do now that he knows that he has the gene for Huntington's disease.

Probably the best way to handle this exercise is to hold a short open discussion in which the students are asked to define the important ethical issues that are involved in each of the questions they are asked to consider, and then have them complete the work sheet as homework. Make it clear that they should explain carefully, in terms of the shared values that they developed as a group, why they believe Roger should or should not share the information with each of the people on his list.

TIMELINE

Probably 15-20 minutes will be adequate for students to read the case and then develop a consensus regarding the issues that it raises. Then on the following day, when students return with their competed worksheets, another 20-30 minutes should be adequate to allow students who answered certain questions differently to discuss their reasons.

Carol and George Face a Tough Decision

STUDENT PAGES 229-231

LESSON OVERVIEW

This case involves a rather different issue than the preceding one. Simply stated, the question is what are the options, and how should choices among those options be made when a young married couple learns that a genetic test indicates that if they have any children there is a one-in-four chance that each child will have a serious, life-threatening disease?

As in the preceding case, the best way to handle this exercise may be to hold a short discussion on the first day about the important ethical issues that are raised by the case, have the students complete their work sheets as homework, and then return on the second day to discuss their opinions and try to reach a consensus.

TIMELINE

Probably 15-20 minutes will be adequate on the first day for the students to read the case and then develop a consensus about the issues that they need to consider. Another 15-20 minutes will be required to discuss the issues and try to reach consensus on the second day, after they have completed the worksheet as homework.

CHAPTER 4

Controlling Our Genetic Futures

SECTION D

DNA in the News

DNA in the News STUDENT PAGE 234

PRESUMABLY YOUR STUDENTS will have been collecting newspaper stories, magazine articles and web items about genetics ever since they began studying the subject. These items can now be exploited in any number of ways to develop a "capstone experience" that will allow students to "pull it all together." Three of the ways that certain teachers have used such materials in the past have are listed below in order of decreasing amounts of your time that they would probably entail. The first two could be joint ventures involving all of your classes. What you choose to do will undoubtedly depend in large part on how much time you have left to devote to the genetics portion of your course.

- **Genetics Jamboree**

  Students will prepare a series of posters and demonstrations to be exhibited in the evening for the benefit of parents, siblings, other classes, school administrators, etc. The posters might be based on articles that have been accumulated on your Genetics Bulletin Board or in your Genetics Scrapbook. The demonstrations might be based on the "hands-on" exercises that the students have performed during their study of genetics.

- **Hallways to Heredity**

  Students will prepare a series of posters to be hung in hallways throughout the school for the edification of students and teachers in other classes. Some of these posters may be based on articles the students have been collecting, but others probably should be designed to introduce others to the basic principles of genetics that your students have learned.

- **Position Papers**

  Individual students or small groups of students will select from the Genetics Scrapbook the articles that they found most interesting, most troubling, most puzzling, or whatever, and will write a position paper that summarizes the content of the article, the important issues that it raises, their own attitudes toward these issues, and where they think this aspect of genetics is (or ought to be) headed.