Cornucopia or Pandora's box? The promise and perils of cloning, genetic engineering, and bioinformatics.

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The revolution in biology is now affecting us routinely. We read on a nearly daily basis about some new finding which may profoundly affect our lives, such as cloning sheep, finding genes which predispose patients to diseases such as alcoholism or certain kinds of cancers, or using DNA sequence data to decide which drugs to use on a particular patient. Many of these findings are highly controversial, and wildly exaggerated claims of both potential benefits and potential hazards have been made. These range from creating monsters or cloning Saddam Hussein to resurrecting dinosaurs, curing cancer and stopping the aging process. In many ways the present situation in biology is akin to the situation in physics earlier this century when physicists learned to split the atom. The genie has been let out of the bottle, with enormous potential for both good and evil, and the question is whether good or evil will predominate. Today I hope to help you understand some of the promises and the perils associated with it.

It is essential that all Americans have some understanding of cloning, genetic engineering and bioinformatics, because we are already profoundly affected by these processes, often without our knowledge. For example, all of you will almost certainly eat some genetically-engineered food this week, because over 32% of corn and 38% of soybeans grown in the U.S. last year were transgenic. However, you won't know it, because in the U.S. genetically-engineered food does not need to be labeled unless its nutritional value or safety has been altered. Since there is no strong evidence that any of the transgenic crops on the market affect the food's nutrition or safety, they remain unlabeled on U.S. produce shelves (27, 29). As another example, DNA evidence is now widely accepted as proof of identity in court cases or other circumstances such as Monica Lewinsky's infamous blue dress or proving that Thomas Jefferson had an illegitimate son by a slave (3). What is not so widely known is that many of you may have your "DNA fingerprints" stored in a national database, especially if you have served in the military since 1992 (14). Many civil libertarians view this as a violation of civil rights, yet on the other hand the military must be able to identify personnel (or what is left of them), and

there are other valid reasons for maintaining genetic databases. There are many other examples of ways that we are already affected by DNA technology but I will stop here because the point is that policy decisions have already been made, and more will be made in the future whether we like it or not. Therefore, it is in our best interests to understand the issues at stake so that we can help ensure that policy decisions are made wisely.

The basis for making rational decisions is knowledge, and what I plan to do is to give you a brief overview of what cloning, genetic engineering and bioinformatics are, how they work, and what can and cannot be done with them. I will then describe some of the social issues that have arisen, and I will conclude by outlining a proposed plan of action for regulating these technologies.

Lets start by defining some terms. Cloning is making identical copies of an object, so cloning a human means making an identical copy of an individual. In fact, this has already been done innumerable times: identical twins are clones. Similarly, cloning a gene means making millions of copies of a particular DNA sequence. Genetic engineering is modifying an organisms genetic makeup in order to improve it in some way. Therefore, cloning and genetic engineering are completely opposite; in the first case we are creating individuals who are genetically identical, whereas in the second case we are creating individuals who are genetically different. The link between the two technologies is that we can use genetic engineering to create a superior organism, and then use cloning technologies to make many copies of it. Bioinformatics is the area of computer science devoted to organizing and analyzing DNA and protein sequences. One especially active area of bioinformatics is devoted to organizing and analyzing the data generated by the human genome project. The purpose of the human genome project is understanding how the human genome works. Its goal is to determine the location, structure and function of all human genes. Currently attention is focused on determining the sequence of the entire human genome and mapping the position of each gene, but this is an intermediate step and the ultimate goal is understanding what each gene does and how it is regulated. Another important area of bioinformatics is the enormous genetic database that is being accumulated on the human population whose purpose, like fingerprinting, is to allow humans to be unequivocally identified.

I will now give a brief description of how cloning, genetic engineering and DNA sequencing and fingerprinting are performed. Cloning entails inducing a fragment of an organism to develop into a new individual; anyone who has ever grown a plant from a cutting has performed a cloning experiment. Many plants are easily cloned; in fact, individual cells of many plant species can be induced to develop into entire plants. Animals have been far more difficult to clone, which is why Ian

Wilmuts report that his group had cloned a sheep raised such a commotion two years ago (31). This was done by removing the nucleus from a sheep egg and replacing it with the nucleus from a mammary gland cell of a mature sheep. They then implanted the resulting embryo into a surrogate mother, who eventually gave birth to a lamb, Dolly, that was genetically identical to the donor of the mammary gland cell. Dolly has proven to be perfectly normal, and in fact has now had a lamb of her own. There were many technical problems to be solved that are beyond the scope of this talk, but subsequently individuals of several mammalian species have been cloned including cows and mice, and attempts are being made to clone several others, including dogs. So, in all likelihood, it should be technically possible to clone humans as well by nuclear transplantation techniques. Limitations to cloning humans are ethical, not technical!

Turning now to genetic engineering, I would first like to remind you that living organisms store their genetic information using a molecule called DNA. DNA is a long chain of building blocks called nucleotides. It consists of a backbone composed of alternating sugar and phosphate molecules, with molecules called bases hanging off the side of each sugar. Information is stored in the sequence of bases much as written information is stored in the sequence of letters. Therefore the order in which they appear is very important. For example, team and meat use the same four letters, but by changing their order they convey a very different meaning. Since there are four different bases the language of genetics is written using a four letter alphabet. Each gene provides the instructions for making a particular protein, along with information telling the cell how much to make and when and where to make it. Genetic engineering relies on our ability to extract DNA, modify it in various ways in a test tube, then introduce the modified DNA into an organism. Genetic engineering in many ways resembles word processing. What is done is to cut the instructions for making a particular protein out of the DNA from one organism and paste it into the DNA of another organism, perhaps after tinkering with it in the laboratory. To do genetic engineering you must first decide which genetic traits to modify. For example, you may wish to correct sickle cell anemia, or improve herbicide resistance. Next, you must identify an organism which has the genes you want, extract its DNA, and clone the DNA sequences which you wish to transfer. Frequently they must be modified so that they will function in the recipient. Once this is accomplished the new genes must be transferred into the recipient. Many techniques for performing DNA transfer have been developed. The easiest to understand is microinjection, where DNA is physically injected into the nucleus of a recipient cell. Another way is to coat little gold pellets with DNA then shoot them into the recipients with a .22 shell, and the easiest way is to trick a virus or other pathogen to do it for you. The final step is identifying the cells which have taken up the foreign DNA. This is usually done by adding a marker gene that clearly identifies cells that have taken up foreign DNA. Most markers

are genes which encode proteins that destroy antibiotics or other poisons and therefore allow organisms to grow in the presence of chemicals which kill all of the organisms which have not taken up foreign DNA.

The human genome project and genetic data bases rely on two technologies: 1) DNA sequencing: determining the order in which bases are arranged on a DNA molecule, and 2) DNA mapping: identifying differences in DNA sequences between individuals and determining the location of these sequences in the human genome. Various techniques have been used for DNA sequencing; the important point is that none can read much more than 300 bases at a time reliably, as compared to the 3,000,000,000 bases in the human genome. This is like making a map of Interstate 80 from New York City to San Francisco one millimeter at a time, using a 300 mm ruler. You end up with an extremely precise map of portions of the genome, but with no idea of where you are overall. To make things worse, many stretches of the human genome are highly repetitive with few distinguishing landmarks, which is like trying to figure out where you are in Iowa or Nebraska and keeping track of what you have measured when you are in the middle of miles of corn fields. Therefore, genome researchers developed techniques for "mapping" the genome so that they know what portion of the genome they are sequencing. Mapping requires identifying DNA sequences which differ between individuals and then determining their position within the genome. This is how DNA fingerprinting arose; once a number of sequences which varied between individuals were found they could be used to identify specific individuals based on the particular combinations of these variable sequences in a given person. DNA fingerprinting was not as easy as it might appear because 99.7 % of the DNA sequences in all humans are identical. It is the 0.3% which varies that makes the differences between us (3). Consequently, identifying sequences which vary and cataloging the extent of variation has been a difficult task, and it seems that every year new types of variable sequences and techniques for measuring them gain favor as the method of choice.

Lets now consider what can be accomplished with these technologies. This list cannot be exhaustive; what I hope to do is point out some obvious possibilities and potential problems. Starting with cloning: in the true sense of the word, all that can be done is to make identical copies of a particular individual. Of course, there are many reasons to do this. One is economic: making many copies of a valuable specimen. For instance, it is currently estimated to cost $60,000 to make a transgenic sheep or goat; therefore, once a good specimen is obtained it is worth cloning (13). A second reason is vanity: one can imagine Saddam Hussein or Ross Perot reeling off dozens of copies of themselves as a gift to the human race. A third reason is replacing loved ones; for example, one might clone a child killed in a car crash if some cells could be kept alive. As a variation on that theme, cloning might also be

used to give children to childless couples. A fourth reason for cloning would be to generate a supply of spare organs for transplants. A fifth reason is to propagate endangered species. Embryo transfer between species has already been used to propagate rare species; for instance, Holstein cows have been used as surrogate mothers for the endangered bongo antelope (3). Therefore, it will not be much of a leap to clone endangered species by nuclear transfer and then propagate them in surrogate mothers of related species. A more far-fetched application is resurrecting extinct species. For example, it may eventually be possible to resurrect woolly mammoths by replacing the nuclei of elephant eggs with the nuclei of cells from frozen woolly mammoths, then transplanting the embryos into elephant surrogate mothers.

Cloning humans raises serious ethical issues. First, cloning is very inefficient, so hundreds of human embryos would die for every success. Secondly, as Ian Wilmut points out, cloning is not good for the cloned child. Parents would expect the clone to develop into an exact copy of the original individual, yet each child will develop in its own manner according to its own life experiences (30). Thirdly, there is the specter of eugenics, where some group attempts creating a master race by using genetic engineering to make a superior individual which is then propagated by cloning. Cloning also raises some practical concerns: for example, populations of identical individuals are prone to epidemics since they are all susceptible to the same diseases. The Irish potato famine of 1845 and 1847 is a classic example of such epidemics.

The initial report of cloning a sheep therefore triggered a tidal wave of legislation aimed at regulating human cloning. Nineteen European countries outlawed it, President Clinton banned the use of federal funds for cloning research, fourteen U.S. states introduced legislation to regulate it, and ten bills designed to ban or regulate cloning were introduced in Congress. However, it proved more difficult to legislate against cloning than originally anticipated, and the senate chose not to vote on a proposed cloning ban when it came on the floor. The problem was that Congress could not agree on how to word a bill that would ban cloning without also banning other types of medical research that many regarded as worthwhile, such as research on growing organs in culture or on human fertility. Moreover, there have been serious challenges to the ban on cloning itself. For example, the American Medical Association issued a statement requesting that human cloning in fact should be allowed, but under close supervision. Similarly, the head of the National Institute of Health was initially adamantly opposed to human cloning, but then changed his mind a few months later. Indeed, although most public sentiment has been anti-cloning, there are also numerous groups promoting cloning. Richard Seed has gained the most notoriety with his public proclamations of his intent to clone human beings (7), but he has competitors. For example, the International Cloning

Society was established to function as an agency for prospective "clonees," and as a lobby for human cloning. Similarly, there is a company based in the Bahamas called Valiant Venture LTD that promises to clone humans for as little as $200,000 (11), and there are recent claims that a group in South Korea has produced a cloned 4 cell human embryo (7). Consequently, it seems inevitable that humans will be cloned unless it is banned worldwide. Indeed, when human *in vitro* fertilization was first developed 20 years ago public sentiment was adamantly opposed to it, yet now it is widely accepted and about 10,000 babies a year are conceived by in vitro fertilization in the U.S. alone. We may therefore find that in twenty years public attitudes towards cloning humans will also have dramatically changed.

Lets now examine genetic engineering. There are currently two major limitations to genetic engineering. The first is that we are limited to transferring at most a few genes at a time and the second is that in many cases we simply dont know which genes to engineer. The reason that we can only transfer a limited number of genes is that each one must function properly in its new environment, and accomplishing this has been very difficult. The problem which arises is that although we know how to interpret the instructions for making proteins, our knowledge of the overall grammar of the genome is very limited. By this I mean that we are becoming increasingly aware that the organization of genes within the genome is very important, just as the way that sentences are organized into paragraphs, paragraphs are organized into chapters and chapters are organized into books profoundly affects the meaning of the book. However, we have only a limited understanding of the higher order organization of genes, other than that it exists and that a gene's location within a genome affects how it works. Therefore, we really dont know where we should put a new gene into an organisms genome, and it is very difficult to control where it goes even if we knew where to put it. To use the word-processing analogy again, we are randomly pasting a block of text into a book and expecting it to make sense. Sometimes it does, sometimes it doesnt, but it will rarely read as well as it did in its original setting. Consequently, randomly inserting several genes into a genome and getting them to all work well is similar to randomly pasting several blocks of text into a book and getting them all to read properly. Turning to the second limitation, in many cases we simply dont know enough about the genetics of a trait to figure out how to usefully modify it. Consider intelligence: presumably this is a trait that many people would like to engineer, yet we cant agree what it is or whether it has a genetic basis.

So what can be accomplished by genetic engineering? Again, there is no way that this list can be exhaustive, but I will touch on some of the highlights. I see three general categories of applications of genetic engineering. The first is basic science: we can improve our understanding of particular genes by modifying them in a test tube and then reintroducing them into an organism. This is especially important now, since genome projects have identified numerous genes of unknown function. The tools of genetic engineering provide the most rapid means of figuring out what they do and how they are regulated.

The second general application is correcting genetic defects. For example, a number of human ailments caused by defective genes have been identified; two which you may have heard of are sickle cell anemia and cystic fibrosis. The idea is to replace the defective copies with a functional version of the gene; the problem is delivering this gene to the cells that need them. Some genes are only needed in a few tissues; in this case it may be possible to isolate some of this tissue, insert the correct gene then reimplant it back into the patient. Several successful applications of this approach have been reported. The first human gene therapy experiment was performed in 1990 on a girl named Ashanthi DeSilva who suffers from severe combined immunodeficiency (SCID, the "bubble boy" disease). SCID is caused by a defective adenosine deaminase (ADA) gene and results in a collapse of the immune system. To correct this defect a team led by W. French Anderson extracted some cells from Ashanthi's immune system and gave them a good copy of the ADA gene. They then injected the modified cells back into Ashanthi, where they proliferated and allowed her to live normally (3). Similarly, a woman with a defect in controlling blood cholesterol levels was successfully treated this way. Some of her liver was removed, grown in culture, and given a good copy of the defective gene. Some of these cells were re-injected into her liver, where they proliferated and helped control her cholesterol (3). An alternative to isolating cells, fixing them and reintroducing them into the patient is to treat the patient directly with "good DNA." For example, lung diseases such as cystic fibrosis have been successfully treated in mice by delivering a good copy of the gene directly to the lungs as an aerosol, and human trials are underway (3). Gene therapy is also being tested as a treatment for AIDS and certain cancers. A variety of different genes are being tested; most are designed to either enhance the body's defenses against cancer or to make cancer cells very sensitive to certain drugs (4). Undoubtedly many more disorders that can be treated by gene therapy will be identified as the human genome project evolves since it is currently estimated that between 2000 and 5000 human disorders have a genetic basis (8). The problem will be devising ways to deliver the good genes to the cells that need them, but it is also nearly certain that an increasing number of disorders will be successfully treated this way in the near future.

A third application of genetic engineering is adding brand-new genes to an individual. Both the potential benefits and potential hazards are high, since a gene is now being placed in a new environment. Many examples of this sort of modification have already been made; these fall into three general categories. The first is to improve resistance of crops or livestock to particular stresses. For example, nu-

merous crop plants have been made resistant to the herbicide RoundUp by genetic engineering; over 38% of the soybeans grown in the US last year were genetically engineered in this way (26, 27, 29). Similarly, many crops have been made more resistant to insects by adding genes for bacterial toxins or plant proteases, and other crops have been genetically-engineered to become more resistant to viral, bacterial and fungal attack by adding suitable resistance genes (3). The second major category of crop or livestock improvement by genetic engineering is to improve their nutritional value, which has been called the nutraceutical approach. For example, leaner pigs have been created by introducing genes for growth hormones which stimulate the pigs to produce more muscle and less fat (3). Similarly, many seed crops are low in certain amino acids, and one solution to this problem is to attempt correcting this imbalance by adding a gene encoding a protein containing large amounts of the missing amino acid from another species (22). As another example, rice grains have recently been genetically engineered to produce beta-carotene, a naturally occurring anti-oxidant that humans convert to vitamin A (6). A third way to improve the value of crops or livestock by genetic engineering is to convert them into reactors producing large amounts of some valuable commodity (22). For instance, plants have been genetically engineered to produce plastics or diesel fuel (20, 24). Similarly, many plants have been genetically engineered to produce edible vaccines: bananas have been engineered to produce vaccines against certain viruses, tomatoes are being used to make vaccines against the rabies virus and potatoes are being used to produce vaccines against cholera (1, 3, 18). This is especially useful for immunizing people in underdeveloped countries, where storing vaccines and transporting them to remote areas are serious concerns. Animals are also being used as reactors: transgenic goats make CFTR protein for treating cystic fibrosis or TPA protein for treating heart attacks, and transgenic cows are used to produce human lactoferrin in their milk (3). In a recent bizarre twist, researchers are using transgenic animals to excrete useful products in their urine which are too toxic to make in other tissues, which means that urine farming may be a new industry in the future (13). Another variation on using animals as "reactors" is to convert them into suitable organ donors for transplants into humans by means of genetic engineering. Organs are in short supply: it is estimated that 8 Americans in need of organ transplants die every day (25). Pigs are considered the best candidates for organ replacements because they are a good match in size and shape and there is little risk of transferring viruses with them. One major problem with xenotransplants is that the human immune system quickly recognizes and attacks the foreign organ. This is where genetic engineering comes into play. Pig organs are rapidly attacked because they contain a sugar called alpha-gal which is attacked by the human immune system, so efforts are underway to remove it by genetic engineering. Another target are proteins called complement inhibitors which prevent our immune system from attacking us; pig organs genetically-engineered to make human complement inhibitors survive much longer

than normal pig organs when they are perfused with human blood. Consequently, we may soon be able to use transgenic pigs as donors for organ transplants (3, 25, 28).

A final application of genetic engineering is to create bioweapons. This is viewed as a very real concern because it has recently been disclosed that the former Soviet Union had a major bioweapons industry, and that Iraq has a similar program. Indeed, Iraq had 20,000 liters of botulinum toxin, 8,000 liters of anthrax spore suspension and had outfitted SCUD missiles with anthrax warheads (10). Ten other countries are also known to be conducting bioweapons research. Moreover, the Japanese terrorist group Aum Shinrikyo made at least nine attempts to aerosolize anthrax and botulism throughout central Tokyo and has sought to obtain Ebola virus for use as a bioweapon. Consequently, the U.S. is thought to be at risk to bioterrorists. Smallpox and anthrax are viewed as the most likely agents, but undoubtedly other biological agents are also being developed (10).

This brings us to the issue of social concerns over genetic engineering. Recently debate has focused on two main issues: the release of genetically-engineered organisms into the environment, and concerns over the safety of genetically-engineered food. Releasing biological weapons is an extreme example of how biotechnology can be misused; however, every release of genetically-engineered organisms into the environment brings with it a certain amount of risk. One problem is the risk of transferring transgenes for things like herbicide resistance to nearby related organisms such as adjacent fields of non-transgenic crops, or to weed species. This is a valid concern because such transfer has been shown to occur. For example, in Germany, corn fields adjacent to transgenic corn were found to have been pollinated by transgenic pollen. This is a problem for organic farmers who claim to be selling a pure, unadulterated product. Moreover, other studies with transgenic rape-seed (*Brassica napus*) have shown that the transgenes can be transferred to the related weed species *Brassica rapa* (21). Consequently, this would soon render the herbicide ineffective. Similarly, many transgenic crops contain antibiotic resistance genes used as markers to identify the transgenic cells. U.S. regulatory agencies have ruled that these genes are harmless, but many European countries disagree. In fact, Norway has banned the import of all plants containing genes conferring resistance to ampicillin on the grounds that this gene may be transferred to harmful bacteria.

Another misgiving about transgenic crops is the effect that they will have on farming practices. One major concern is that they will tend to encourage the overuse of dangerous chemicals such as RoundUp, with potential environmental consequences of the accumulation of such chemicals in soils and water. This also selects for weeds or insects which are resistant to the chemical. A second major concern is

that seed companies and researchers will focus on solving agronomic problems by means of genetic engineering and will ignore research in other areas such as biological control. This neglect of alternative forms of pest control may result in major outbreaks of diseases owing to the reduced biodiversity. A third concern is that these new plants will cost too much for subsistence farmers in under-developed countries to buy. Monsanto's recent development of what opponents have called "terminator technology" does nothing to alleviate these worries. This technology is designed to force farmers to buy new seeds each year by making the seeds produced by these plants sterile. Consequently, there is a growing resistance to genetically-engineered plants in third world countries. Indeed, there is a precedent justifying their skepticism. Although the high yield crops developed in the 1960's have doubled grain production worldwide since that time, they did not work as well as predicted in under-developed countries owing to the requirement for expensive equipment and intensive use of fertilizers and pesticides (2, 5, 17). Many people are therefore concerned that a major consequence of using genetically-engineered crops will be to put yet more farmers out of business.

In the U.S. concerns over the release of genetically-engineered organisms have died down after the furor raised in the 1980s by the tests in California of bacteria which had been genetically-engineered to reduce frost damage to strawberries. However, they are rampant in Europe, and last summer protesters in Germany, France and Britain cut down fields of transgenic crops. Norway, Austria and Luxembourg have banned the import of transgenic crops containing antibiotic resistance genes, and last year France revoked the permit given to Novartis to grow transgenic corn in France. In England, Prince Charles has publicly voiced his opposition to genetic engineering and has established on on-line forum to discuss the issue (12). In fact, this February the United Nations sponsored a meeting in Cartagena, Colombia to attempt creating an International Biosafety Protocol to regulate issues related to biotechnology such as the transport of transgenic organisms and labeling of transgenic foods. Although the accord was approved by more than 125 nations including the entire European Union, it was scuttled by the United States and Australia, Canada, Uruguay, Argentina and Chile on the grounds that it would be overly restrictive to international free trade.

One reason that the U.S. torpedoed the treaty was that it called for the labeling of all transgenic food. Genetically-engineered food has received little attention in the U.S. after the initial release of the Flavr-Savr tomato in 1994; as I stated at the beginning of the talk, most of us are blissfully unaware of the fact that we are eating transgenic foods daily. One reason is that the federal agencies involved in regulating food do not require labeling unless the genetic engineering alters the nutritional or safety status of the food. Cynics feel that this is largely because these agencies are controlled by the companies like Monsanto which created the prod-

ucts, since 81% of Americans believe genetically-engineered food should be labeled as such, and 58% of Americans would not buy genetically-engineered food (27).

However, most of the world disagrees with the U.S. on this issue. The 125 nations that signed the International Biosafety Protocol believe that all transgenic foods should be labeled and segregated from non-transgenic food. In Europe protests against transgenic food have become increasingly strident. For example, in England there have been massive protests staged by Greenpeace in England protesting the import of American genetically-engineered soybeans. Among other activities, Greenpeace protesters delivered 4 tonnes of genetically-engineered soybeans to 10 Downing Street, the address of the British prime minister, Tony Blair, stating that he was the only Briton who wanted them. Similarly, there is currently a scandal over data indicating that a diet of transgenic potatoes caused intestinal damage in rats and adversely affected their growth. Accusations that the data was suppressed by the research institute and by the government have aroused a great deal of controversy in Parliament. On the continent, last fall protesters cut down 4.5 tonnes of transgenic corn in France and Germany and delivered it to Novartis headquarters in Basel, Switzerland. In fact, Greenpeace demanded an immediate ban on genetically engineered foods on February 12 of this year. Consequently, genetically-engineered foods face a major uphill battle in Europe. Some of the fears stem from the recent scare over mad cow disease in Britain, some stem from legitimate concerns that there has not been adequate testing of long-term effects of genetically-engineered food, and some stems from paranoia and complete misunderstanding of genetic engineering. Nonetheless, these concerns need to either be alleviated or American farmers need to reconsider planting transgenic crops, because Europe is one of the major markets for these crops and there is a real danger that they will be banned outright.

I will now turn to bioinformatics. We already have a vast amount of human sequence data, and the complete sequence will be available within a few years. This has already provided a treasure trove of information about the structure and function of the human genome, and far more is undoubtedly forthcoming. There are also many potential clinical applications of this information. For example, doctors (or pharmacists) will be able to match specific drugs with specific patients. They will also be able to tell by DNA testing whether there is a genetic basis for a patients ailment, or whether a patient is at risk of developing a particular condition. Unfortunately, insurance companies or employers will be able to use DNA sequence information for exactly the same purpose, and use this information to decide whether to insure or hire an individual. So, in a sense, DNA sequence information is similar to other sensitive personal information such as your credit history, with the added complication that it is especially vulnerable to misinterpreta-

tion. One thing that is inadequately appreciated is that interpreting genetic data is often very tricky. Many genes predispose the carrier to a disorder; whether or not carriers develop the disorder depends on the rest of their genetic makeup, the environment they live in, their lifestyle and pure dumb luck. Will insurance companies or employers recognize this, or will they simply view the presence of certain genes as grounds for dismissal? In fact, since we are all different, how will we define a "normal" gene? Will it be the most common version, the one shown to encode the "best" protein, or some other criterion, and who will make that decision?

Consequently, a very important issue currently faced by our society is deciding who should have access to our DNA sequence information, and how it should be used. In fact, a Time poll showed that 95% of Americans believe that employers and insurance companies should not have access to this data (16). On the other hand, about two thirds of the respondents did want to know if they or their children were at risk of developing certain disorders (8). Because of these considerations there are 20 bills before Congress regarding genetic procedures, 30 states have passed laws prohibiting genetic tests on job or insurance applicants, and at least 70 more genetic-discrimination bills are pending in 24 states (9).

A related issue is the ownership of genetic information. In the U.S., debate has largely focused on whether anyone should be allowed to patent genes. According to a Time poll published in the January 15, 1999 issue, 71% of Americans disapprove of private companies being allowed to patent human genes in order to make money (23). In fact, a number of human genes have been patented already, many by the U.S. government itself (15, 16). However, the U.S. is once again out of step with much of the rest of the world on this issue. A new industry called bio-prospecting has recently evolved in which the prospectors go to remote areas of the world to track down and patent useful biochemicals. Many underdeveloped countries view this as genetic imperialism or gene piracy, where wealthy nations are coming to plunder them of a form of wealth which they are currently unable to develop for themselves (19). Again, this has not received much attention in the U.S., but it is a major bone of contention elsewhere. Indeed, part of the purpose of the International Biosafety Protocol referred to earlier was to regulate patenting of biological materials, and, as stated earlier, the U.S. is one of the few nations which refused to ratify it. A major concern is that with modern technology it is very simple to smuggle DNA samples out of a country, and it will be extremely difficult to identify the origin of a new wonder gene. Consequently, many groups are seeking ways to protect the biological rights of developing nations. One approach, taken by Costa Rica, is to get companies to help inventory the biological diversity in the nation in exchange for a share of the potential payoff. Other countries are considering a more drastic approach: to evict the bio-prospectors until a means is developed to return some of the profits to the country the genes came from.

The final topic which I will discuss is the use of DNA for identification purposes. In the U.S. both the Department of Defense and the FBI are collecting databases of DNA fingerprints to be used to identify humans. The Department of Defense database is to be used to identify military personnel, whereas the FBI is storing the DNA fingerprints of 250,000 convicted felons. A similar data base operates in England, where over 360,000 DNA fingerprints are on file. DNA fingerprinting has been very effective: the FBI claims that it has already used it to crack 200 outstanding cases. However, DNA fingerprinting raises the ire of the ACLU since it is in many ways the ultimate intrusion on privacy, and because there is the possibility of adding law-abiding citizens to the database. In fact, in December 1998 the New York City police commissioner proposed that DNA samples should be collected from anyone ever arrested (15). However, on the positive side, DNA testing has also exonerated many suspects, and at least 10 death-row inmates have been released based on DNA evidence. Similarly, such a database will be invaluable in identifying humans or human remains after especially gruesome accidents. In fact, in the near future we may find that authorities turn to the doctors for tissue samples rather than to the dentists for dental records when attempting to identify human remains. This may not even be necessary; DNA gathered for medical purposes such as drug matching may also be sufficient to positively identify the donor. Consequently, just as with other DNA data, the issue to be resolved is who should have access to such data, and when.

In summary, cloning, genetic engineering and bioinformatics have an enormous potential for both good and ill; the outstanding question is how to deal with it. Unfortunately, the human race has shown time and again that it has a tendency to leap before it looks, and therefore I think that there is a need for caution and close supervision. For example, I think that the use of herbicide and insecticide resistance genes to control pests is almost guaranteed to cause severe problems within a few years. We have already seen what happens when antibiotics are overused; you simply end up with new strains of bacteria that cant be killed. I therefore believe that within a few years both the herbicide and the insect resistance genes will be useless, and we will have major accumulations of herbicides to contend with as well. In my opinion, this is yet another example of large companies placing short-term profits ahead of environmental considerations. On the other hand, the potential benefits of DNA technology are great enough that it would be foolish to simply ban it outright. Therefore, to me the best solution is a benevolent dictatorship. A regulatory commission composed of both biologists and lay people should be formed and given absolute authority over genetically-enginered food and all releases of genetically-engineered organisms. The purpose of the biologists will be to ensure that the transgenic organisms are not a threat to humans or to the environment; there should therefore be a mix of genetic engineers, physiologists

and ecologists. The purpose of the lay people will be to represent the concerns of the public and to address legal and ethical issues. These should therefore include lawyers, bioethicists and sociologists. One major charge of the commission will be to educate the general public about genetic engineering so that the public is aware of what the benefits and hazards really are. Another charge of the commission will be to solicit public opinion so that it can address issues such as concerns over labeling transgenic food or the release of organisms containing antibiotic-resistance genes. In this way we can hopefully ensure that progress will be allowed, but in a controlled fashion that is responsive to public opinion.

Similarly, human genetic data has too many worthwhile uses to be outlawed, yet the potential for abuse is equally prevalent. Therefore, federal regulations governing the acquisition and dissemination this data need to be passed and rigorously enforced. I also think that patenting genes obtained from natural sources should be outlawed; at least, until mechanisms are developed to ensure that the countries or ethnic groups that the genes came from can share in the profits.

However, there is no doubt that the coming century will see increasing use of cloning, genetic engineering and bioinformatics. Since we cant put the genie back in the bottle, lets embrace the future and learn how best to use it for our advantage.

Literature Cited

1) Arakawa, T., Chong, D.K., Hough, J., Engen , PC,and Langridge, W. H. R. (1998) A plant-based cholera toxin B subunit-insulin fusion protein protects against the development of autoimmune diabetes. *Nature Biotechnology* **16**: 934-938

2) Audesirk, T. and Audesirk, G. (1996) Biology: Life on Earth. (Prentice Hall, Upper Saddle River, New Jersey), 947 pp.

3) Barnum, S. R. (1998) Biotechnology. (Wadsworth Publishing Company, Belmont, CA), 225 pp.

4) Blaese, R. M. (1997) Gene therapy for cancer. *Sci. Am.* **276**: 111-116

5) Brookfield, H. and Byron, Y. (1993) South-East Asia's Environmental Future: the Search for Sustainability. (Oxford University Press, Oxford), 452 pp.

6) Burkhardt, P. K., Beyer, P., Wunn, J., Kloti, A., Armstrong, G. A., Schledz, M., et al. (1997) Transgenic rice (*Oryza sativa*) endosperm expressing daffodil (*Narcissus pseudonarcissus*) phytoene synthase accumulates phytoene, a key intermediate of provitamin A biosynthesis. *Plant J.* **11**:1071-1078

7) Cole, W. (1999) Seed of controversy. *Time* **153(1)**: 77

8) Golden, F. (1999) Good eggs, bad eggs. *Time* **153(1)**: 56-59

9) Hallowell, C. (1999) Playing the odds. *Time* **153(1)**: 60

10) Henderson, D. A. (1999) The Looming Threat of Bioterrorism. *Science* **283**: 1279-1282.

11) http://www.clonaid.com

12) http://www.princeofwales.gov.uk/forum/

13) Kerr, D. E. (1998) The bladder as a bioreactor: Urothelium production and secretion of growth hormone into urine. *Nature Biotechnology* **16**: 75-79

14) Kluger, J. (1999) DNA detectives. *Time* **153(1)**: 62-63

15) Kluger, J. (1999) Who owns our genes? *Time* **153(1)**: 51

16) Lemonick, M. D. and Thompson, D. (1999) Racing to map our DNA. *Time* **153(1)**: 44-50

17) Mann, C. C. (1999) Crop scientists seek a new revolution. *Science* **283**: 310-314

18) Mason, H. S. and Arntzen, C. J. (1995) Transgenic plants as vaccine production systems. *Trends Biotechnol.* **13**: 338-392

19) McGirk, T. (1998) Gene piracy. *Time Asia* **152(18)**: http://cgi.pathfinder.com/time/asia/magazine/1998/981109/cover1.html

20) Poirier, Y., Dennis, D. E., Klomparens, K. and Somerville, C. (1992) Polyhydroxybutyrate, a biodegradable thermoplastic, produced in transgenic plants. *Science* **256**: 520-523

21) Snow, A. A. and Moran-Palma, P. (1997) Commercialization of transgenic plants: potential ecological risks. *BioScience* **47**: 86-96

22) Stark, D. M., Barry, G. F. and Kishore, G. M. (1993) Impact of plant biotechnology on food and food ingredient production. in: Science for the food industry of the 21st Century. M. Yalpani (ATL Press, Mount Prospect, Illinois), 115-132

23) Thompson, D. (1999) Gene maverick. *TIME* **153(1)**: 54-55

24) Töpfer, R., Martini, N. and Schell, J. (1995) Modification of plant lipid synthesis. *Science* **268**: 681-686

25) Travis, J. (1995) The Xeno-Solution: Perils and promise of transplanting animal organs into people. *Science NewsOnline: http://www.sciencenews.org/sn_edpik/ms_4.htm*

26) Walsh, J. (1998) Alien seed. *TIME International* **152(8)**: http://cgi.pathfinder.com/time/magazine/1998/int/980824/cover_story.alien_seed19a.html

27) Walsh, J. (1999) Brave new farm. *TIME* **153(1)**: 86-88

28) White, D. (1996) Alteration of complement activity: a strategy for xenotransplantation. *Trends Biotechnol.* **14**: 3-5

29) Williams, N. (1998) Agricultural biotech faces backlash in Europe. *Science* **281**: 768-771

30) Wilmut, I. (1999) Dolly's false legacy. *TIME* **153(1)**: 74-77

31) Wilmut, I., Archibald, A. L., McCleghan, M., Simons, J. P., Whitelaw, C. B. A. and Clark, A. J. (1997) Viable offspring derived from fetal and adult mammalian cells. *Nature* **385**: 810-813

Concerning the Speaker

Dr. William Terzaghi received his Ph.D. in plant cell biology from the University of Utah, followed by post-doctoral training in plant physiological ecology at the Carnegie Institution of Washingtons Department of Plant Biology on the Stanford campus. Dr. Terzaghi next learned plant molecular biology in the Plant Science Institute at the University of Pennsylvania, before joining Wilkes in the fall of 1995. At Wilkes he has taught introductory biology and several upper level courses in cell and molecular biology. He has also established a research program in plant molecular biology funded by the U.S. Department of Agriculture which currently involves 16 undergraduates.

Dr. Terzaghi has a diverse background. Although born in the U.S, he went through sixth grade in Kobe, Japan and then moved to Geneva, Switzerland. The portion of this trip from Karachi, Pakistan to Geneva was driven overland in a Land Rover, traveling through Afghanistan, Iran, Turkey, Greece,Yugoslavia and Italy. After three years in Geneva he returned to the U.S., finished high school in Santa Cruz, California and spent one year at Reed College (as a French Literature major) until wanderlust struck again and he moved to New Zealand. The move to New Zealand involved another three month trip in the Land Rover, this time driving through Central and South America. Once in New Zealand he spent four years working at various jobs including logging, deer hunting, shearing (his New Zealand shearers certificate sits above his office telephone as a reminder of the good old days), ski instructing and several stints at various construction sites. Eventually he obtained a bachelors in Biology from the University of Waikato in Hamilton, New Zealand, although he managed to sneak a four month trip to Mexico and Central America in beforehand. Owing to the offset in academic years between the Southern and Northern hemispheres he also spent five months in Europe between finishing his bachelors degree and starting graduate school. Thanks to all this traveling he is fluent in French and also speaks Spanish and German reasonably well.Dr. Terzaghi lives in Kingston with his wife Vivien, his children Nadia and Damon, three dogs, two cats, three guinea pigs and numerous fish. When he can find the time he enjoys running, skiing, kayaking, climbing and fishing.

Concerning the Lecture

The premise of the Final Word Lecture is that the lecturer has only six months to live and would like to sum up a career of teaching and scholarship for colleagues, students, and friends. While the selected professor is, in fact, healthy, the hypothesized death adds urgency and focus to the lecture. The idea is borrowed from the University of Michigan's "Last Lecture."

The Final Word Lecture is given on the evening of Wilkes University's Faculty Recognition Day, at which faculty are lauded for their achievements as teachers and scholars. A number of awards, including the Carpenter Award for teaching, are announced at this annual event.

The Final Word lecturer is chosen by a committee of Wilkes professors and receives a $1,000 award through the generosity of an anonymous donor. At a subsequent time, and at the donor's discretion, the title of the award and lecture series will be changed to include the donor's name.

Previous winners were:

1993 James L. Merryman
Reinventing Humanity for Survival in the Twenty-first Century: Salvaging Our Best through Prehistory and Multiculturalism

1994 Dennis P. Hupchick
Nation or *Millet?* Contrasting Western European and Islamic Political Cultures in the Balkans

1995 Donald R. Brand
Multiculturalism Revisited

1996 No lecture given

1997 Jane M. Elmes-Crahall
Rhetorical Savvy and Political Civility

1998 Patricia Siplon
Scholar, Witness or Activist: The Lessons and Dilemmas of an AIDS Research Agenda