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INTERFACE:
GENES AND THE ENVIRONMENT

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Family Genetic Information: Who Has the Right to Know?

For each of the approximately 31,000 genes in our DNA, we inherit one ***allele*** from our mother and one allele from our father. Although every gene has evolved because of a function that is useful to the organism, some allelic variants in particular genes lead to specific diseases. "Disease-linked genes" include everything from phenylketonuria, cystic fibrosis and Huntington disease, to enhanced risk of coronary artery plaques, Alzheimer dementia, arthritis and cancer. For the first two of the above-mentioned diseases, one must inherit a "malfunctioning allele" of a particular gene from both the mother and the father**;** this mode of inheritance is termed ***autosomal recessive***. Huntington disease occurs when a person inherits a defective allele of the *HD1* gene from either the mother or the father**;** this mode of inheritance is termed ***autosomal dominant***. The other four disorders represent "complex diseases" in that they are caused by the interaction of numerous genes with environmental factors.

IN THIS ISSUE

Knowledge about the occurrence of certain disease-linked alleles among family members can help individuals to take action aimed at preventing or delaying the onset of such disease. The health care provider (or other reliable health information source) may suggest preventive actions for persons who are considered to have an increased hereditary risk for a particular disease. Preventive measures include**:** a specialized diet, frequent medical check-ups, avoidance or altered dosage of certain drugs, and avoidance of particular types of environmental exposures (e.g. cigarette smoke, chemicals in the work place, etc.). In this way, the age of onset for a specific genetic-related disease may be extended, the symptoms stemming from the disease may be lessened, and/or the disease might even be prevented. An example of this kind of prevention would be a phenylalanine-free diet to prevent mental retardation in young children with phenylketonuria. Another example of prevention would be a low-fat diet, plus cholesterol-lowering drugs for persons who have genetically high cholesterol levels.

You Have Rights about Your DNA

Whereas medical knowledge of inherited tendencies can be useful, there are issues involved in obtaining information related to which alleles you have (your specific ***genotype***). Regarding genetic information, the major concern these days has to do with the protection of individual privacy.

For very good reason, you should be concerned that an employer or health insurance company might find out about your having a disease-linked allele and

decide to use this information for discriminatory purposes. This could result in your loss of a job or loss (or greatly increased price) of your medical insurance policy. Therefore, the person who has such an allele should have the right to decide whether anyone else needs to know about this information. Moreover, you should have the power to decide for yourself whether to sign a release before this information can be made available to others. Obviously, ***the more you know*** about the fundamentals of science and genetics, the more prepared you will be to make such a decision.

Other Family Members Have Their Rights

What constitutes a "family member" and what are their rights? A child's parents and siblings are called ***primary*** relatives because they share one-half their DNA (***Figure 1***). ***Secondary*** relatives share one-fourth of their DNA, and ***tertiary*** relatives share one-eighth of their DNA. Even if only one-eighth of your DNA is shared with a family member who was diagnosed with a serious life-threatening disease, wouldn't you want to know if that gene has been passed on to you?

Therefore, there are several issues involved in sharing the information about a patient's specific genotype with other family members. In the case of testing for genetic susceptibilities, there might not necessarily be any "legal right" for the spouse of the person involved to receive that information. On the other hand, there would be moral grounds for the individual in question to reveal such information to a spouse if, for example, the problem could possibly lead to the birth of child with mental retardation or any other serious hereditary condition. This situation would seem similar in scope to that of informing one's spouse-to-be about being sterile or having a sexually transmitted disease (if you know it).

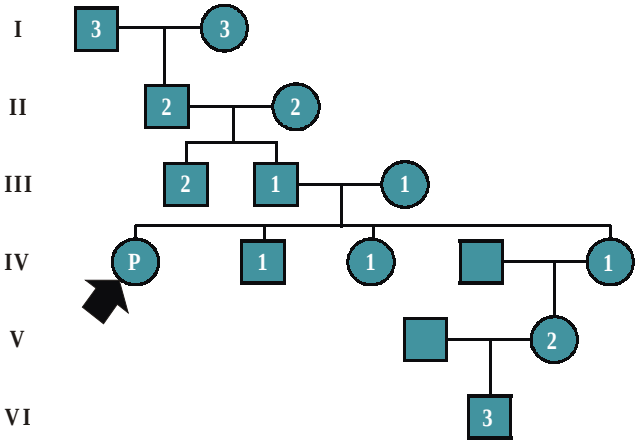

Figure 1. A hypothetical 6-generation family tree. Squares and circles represent males and females, respectively. Propositus (**P**) with arrow is the reference individual, meaning the patient first discovered which then led to the family study. Primary relatives of the propositus are denoted with "1," secondary relatives with "2," and tertiary relatives with "3."

All individuals have the right to decide whether to share genetic information with primary (or secondary or tertiary) family members. In a court of law, a son or daughter may be declared as not having a right to receive information about the results of DNA testing performed on his or her parents. A positive test for a disease-linked allele may create conditions that would exert social pressure on other family members to also be tested. This could be particularly distressing if blood relatives do not want to know their own genetic make-up. Some of these issues were discussed with four court examples in issue #10 of ***Interface*** (winter 1997) and are summarized in an abbreviated form in ***Table 1***.

Parents, the Adopted Child, and Birth Parents Have Their Rights

More and more adoptions have occurred in the U.S. in recent decades. A moral dilemma surrounds the rights of adopted children (and also the parents who adopt such children) to obtain genetic information about the birth family. Adoption laws have been passed to protect the rights and interests of the children, birth parents and adoptive parents. State laws assure citizens access to records contained in state agencies and department files pertaining to themselves**;** these laws guarantee that "this information will be withheld from other parties whenever its disclosure would clearly constitute an invasion of privacy." On the other hand, rules and regulations about privacy matters regarding adoption and the release of information vary greatly from state to state.

The adoptive family and the child, especially as time passes, may need to know the background and medical history of the birth mother and birth father (if known). For example, what if the adopted child develops schizophrenia, manic depression, or a type of neurological disease as an adolescent? What if one of the birth parents has the specific allele for increased risk of Huntington disease? This serious disorder, leading to a decline in quality of life and

Table 1. Examples of ethical issues in human genetics*

Case #1: A patient with thyroid medullary cancer dies 2 years after diagnosis. Her eldest daughter develops the same disease 3 years later, but the cancer is already advanced. She sues her mother's physician, claiming that the doctor "should have told her that this disease is transmitted as a dominant trait," which gives the daughter a 50% chance of developing the disease. An early warning from the physician to the daughter might have saved her life.

- The Florida Court ruled that, in the usual doctor-patient relationship, the physician has no legal obligation to speak with other members of the family about their risks.

Case #2: A patient with adenomatous polyposis coli (APC; multiple tumors of the colon) is diagnosed in 1958 and treated until his death in 1964. His physician dies in 1969. The patient's daughter develops the disease in 1989 and sues the doctor's estate in 1995, claiming that the physician should have informed her of the 50% likelihood of her developing this autosomal dominant disease.

- The Florida Court ruled that, despite the earlier decision in Case #1, it may sometimes be obligatory for the physician to communicate important genetic information to family members concerning the likelihood of children or other primary relatives to develop a serious medical condition.

Case #3: A 25-year-old professional woman is injured so severely in an automobile accident that she is unable to work for the rest of her life. She sues the driver of the other car for negligence. If she works until retirement at age 65 and makes, on average, $100,000 per year, it can be calculated that she is able to earn $4 million over a normal lifetime. However, her father has Huntington disease—meaning that the patient has a 50% chance of developing this dominant disease, which, on average, affects people by age 50. If she carries the defective *HD1* allele, this would reduce her lifetime earnings to ~$2.5 million. The insurance company therefore wants her to be tested, but she does not want to know whether she is an *HD1* carrier (as is true of almost 90% of all children who have a parent diagnosed with Huntington disease).

- The Minnesota Court ruled that she was legally obliged to have the genetic test.

Case #4: Early in her pregnancy, the patient asks her physician for the fetus to be tested for the *HD1* allele. Although her side of the family has no Huntington disease, her husband's father died from this. This means that her husband has a 50% risk of carrying the *HD1* allele, but he does not want to know his genotype. If the test of her fetus is positive, she confides in her doctor that she would then want to terminate the pregnancy and simply tell her husband that she had had a spontaneous miscarriage.

- What is the physician to do? What should the medical counselor do? If the health care provider agrees to join in deceiving the husband, what consequences might result in the future?

*These examples were given during a November 1996 lecture at the University of Cincinnati, by Mark A. Rothstein, JD (at the time, Professor & Director of the Health Law and Policy Institute, University of Houston). Currently, Mr. Rothstein is the Herbert F. Boehl Professor of Law (Louis D. Brandeis School of Law) and Professor of Medicine at the University of Louisville, Kentucky.

early death usually manifests itself between the age of 40 and 60**;** because it is inherited as an autosomal dominant trait, this means that the adopted child would have a one-in-two risk of developing Huntington disease. With the knowledge of having the allele associated with Huntington disease, perhaps the adopted child would choose to have no children.

Prior to adoption, the birth parent(s) usually fill(s) out a social and medical history. This information may be shared with the adoptive parents before the child is placed with them. Because most birth parents—like most of the public-at-large—have not yet had genetic testing, this type of information does not usually appear in medical histories. To the extent that DNA tests are becoming more common, however, it is increasingly likely that genetic information will appear in the medical histories of adults and, probably, this information would not be withheld.

Again, states should have some latitude in their interpretation as to whether the revealing of this information would be a violation of privacy. One reason that may be justifiable for opening sealed records is the "need to know." If, at some time in the future, DNA testing for hereditary susceptibilities becomes more common, and if sons and daughters are given legal rights to access their parents' genetic information, then adopted persons would also have convincing arguments for opening sealed medical records.

The case can also be made that family traits—at the level of DNA—are not always relevant. In other words, how much is ***nature*** and how much is ***nurture***? Although a child's genetic make-up is half from each parent, many complex characteristics are the result of a particular combination of alleles from

numerous genes, some from the mother and others from the father. Thus, DNA testing is the easiest (and only valid) way for an individual to know about his or her combination of alleles and, consequently, identify the level of risk for any particular complex disease.

Finally, it must be emphasized that "having a risk" and "developing the disease" are two different things..! "Risk" translates into probability (e.g. if we drive 12,000 miles to work each day for a year, what is the probability that we will experience an automobile accident? what is the risk of being injured? of being killed during this next year?). Not all people who test positive for a disease-linked allele will develop the disorder. Those who test positive can simply be described as having a "genetic risk factor," a propensity, which increases their probability of developing a particular disease. Further education on these matters would benefit all of us as patients and family members. Further education also comprises essential knowledge for judges, lawyers and legislators who make the laws and pass judgments based on these laws.

————Contributed by Susan Vandale[1], Eula Bingham[1], Nancy Steinberg Warren[1], and Dan Nebert[2]; [1]Community Outreach and Education Program (COEP), CEG ; [2]Ecogenetics Research Core, CEG

Suggested Reading:

- **Rights and Responsibilities of Birth Parents, Prospective Adoptive Parents, and Adoption Agencies (The Commissioner's Statement on Completing an Adoption in Minnesota) http://www.crossroadsadoption.com/responsibilities.html**
- **The Medical Need to Know: Some states allow the birth parents to include a medical report in the relinquished child's file. http://www.howtoinvestigate.com/download/adoption.htm**

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We WELCOME these UC researchers to the CEG

Stephen Daniels, MD, PhD, *Professor, Departments of Pediatrics and Environmental Health*

Stephen Daniels, in the Children's Hospital Medical Center, specializes in pediatric cardiology. His research focuses on understanding the development of risk factors for adult cardiovascular disease in pediatric populations. His studies aim to understand the blood pressure elevation and cholesterol abnormalities in children, and the role of obesity and environmental and life style factors in the progression these diseases. SDaniels@CHMCC.org

Susan Pinney, PhD, *Associate Professor, Department of Environmental Health.*

Susan Pinney has joined the Genetic Epidemiology and Biostatistics F&S Core and will lend her expertise to the CEG on population and clinical studies, developing tracking methods for data and specimen collection, locating and obtaining archived tissue specimens, and implementing appropriate quality control procedures in field studies. susan.pinney@uc.edu

Yolanda Sanchez, PhD, *Assistant Professor, Department of Molecular Genetics*

The primary aim of her research is to investigate the signal transduction pathways that regulate the cellular responses to DNA damage and replication interference, in particular, understanding mechanisms which sense DNA damage and the response in the cell cycle. A long-term goal of this work is the generation of mouse models to study the role of checkpoint components in development and cancer. She makes use of the complementary mammalian and budding yeast systems to define the protein machinery involved in both the DNA damage checkpoint and DNA repair processes. sanchey@uc.edu http://www.molgen.uc.edu/cv/sanchez/sanchez.html

Laughing helps, it's like jogging on the inside.

CEG Members in the News

Eula Bingham received the first David P. Rall Award for Advocacy in Public Health - memorializing the former National Institute of Environmental Health Sciences and National Toxicology Program director who died following an automobile collision in France last year. The award was made by the American Public Health Association to Dr. Bingham for her lifetime of work, including being Assistant Secretary of the Occupational Safety and Health Administration from 1977 to 1981. The award was made at the opening of the American Public Health Association's 128th annual meeting (Boston, November 2000). The National Research Council of the National Academy of Sciences, Division on Earth and Life Studies, has asked her to serve as an advisor for a 2-year term.

Grace Lemasters was awarded a training grant for a "Molecular Epidemiology in Children's Environmental Health Training Program," which is an interdepartmental and interdisciplinary effort to equip outstanding predoctoral, and postdoctoral MDs and PhDs with the knowledge to undertake epidemiological and clinical studies using molecular markers of exposure, effect and susceptibility.

Daniel Nebert was an invited speaker in the session on "New Concepts in the Field of Drug-Metabolizing Enzymes**:** Pharmaco- and Toxico-Genomics," at the 13th International Symposium on Microsomes and Drug Oxidations, Stresa, Italy (July 2000)**;** an invited contributor at the Human Gene Nomenclature Workshop and the HUGO Mutation Database Initiative Meeting, satellite meetings of the Annual Meeting of the American Society of Human Genetics, Philadelphia, Pennsylvania (October 2000)**;** and an invited speaker at Cambridge Healthtech Institute's 2nd Annual "Pharmacogenomics: A New Script for Prescriptions" Conference, Philadelphia, Pennsylvania (October 2000).

Nancy Steinberg-Warren has received two awards to support an education outreach about folic acid in the "Every Child Succeeds Program." She was also elected as the Accreditation Chair, American Board of Genetic Counseling (January 2001). She gave three poster/platform presentations at the National Society of Genetic Counselors (November 2000)

Daniel Woo was recently awarded an NIH K-23 clinical research training grant for the next 5 years. The "Familial Aggregation of Stroke" study will examine the prevalence of traditional stroke risk factors among families with high incidence of stroke. These funds will also allow him to pursue a masters of science in molecular genetics and graduate level course work in genetic epidemiology.

I've learned ... that opportunities are never lost; someone will take the ones you miss.
....Andy Rooney

CEG Workshop

The CEG held a workshop in November 2000 entitled ***"Steroid Receptors and Cell Signaling"*** *which was co-sponsored by the Signal Transduction Research Core of the CEG. The symposium presented cutting-edge research related to the function/dysfunction of estrogen and androgen receptors and the role of these receptors in signal perception, signal transduction and control of cell proliferation. The keynote speaker was Jan-Åke Gustafsson, who spoke about the ying-yang theory of estrogen receptors alpha and beta signaling. Other speakers included Cheryl Walker, John McLaughlan, Christian Grohé, Chaushang Chang, Karen Knudsen, and CEG members Sohaib Khan and Nira Ben-Jonathan.*

Gene Number and Superiority?

Many scientists have believed that, somehow, the number of genes in the human genome must be the secular equivalent of the soul. What has unfolded (read on**..!**) would suggest that the human soul is much, much more.

The Human Genome Project, which began in October 1990, has been sufficiently completed insofar as we found out the approximate "total number of genes" before the end of 2000. "Genome" refers to the DNA content in any living cell. Each virus, bacterium, plant or animal has its entire gene complement in every cell. It is simply that "genes turned on" in one cell differ from those turned on in another cell—which explains why a nerve cell differs from a liver cell differs from a tumor cell differs from a cell that is part of an oak tree root or the petal of a petunia. Since 1995, some 30 bacterial genomes have been completely sequenced and another 100 are known to be in progress. The total gene number in any of these ranges between about 1,200 and almost 6,000. For example, *Hemophilus influenzae*, a common cause of children's ear infections, has 1,743 genes**;** *Mycobacterium tuberculosis*, the bug responsible for tuberculosis, has about 4,000 genes.

In 1996, common baker's yeast (*Saccharomyces cerevisiae*) was found to have 6,200 genes; this was the first "diploid" (having pairs of chromosomes, instead of a single chromosome like bacteria) living thing to have its genome completed. In 1998 the tiny roundworm (nematode) about 1-2 mm in length (*Caenorhabditis elegans*) was discovered to have 19,099 genes. The following year came the fruit fly (*Drosophila melanogaster*), with legs and wings and eyes (things the roundworm does not have), with a suprisingly low number of genes**:** about 13,500. Last autumn was reported the first complete sequence of a plant genome, *Arabidopsis thaliana* (a small mustard plant), and it has at least 25,498 genes.

Based on these numbers, how many genes would we expect for the highly intelligent human being..? A musician like Mozart, a poet like Shakespeare, a mathematician like Einstein, or someone who speaks a dozen languages fluently? 100,000 genes? 500,000? a million?—that would be the "natural" thing to expect. As mentioned in an earlier issue of ***Interface***, Incyte, a California-based biotechnology company estimated in 1999 that humans would have 142,600 genes. But, the Human Genome Project summary report (which formally appeared in February 2001) was staggering**:** *Homo sapiens* has about 31,000 genes, barely more than a tiny mustard plant. And it is now very likely that some plants (rice and the ornamental lily, *Fritillaria*) are good candidates) will be found to have more genes than human beings [*Science* **290:** 2054, 2077, 2000]**..!!**

"Q"uote of the Month.....

Good judgment comes from experience, and a lot of that comes from bad judgment....

Will Rogers, 1879-1935

Genomically Speaking, ...

What follows is a synopsis of some of the more interesting things that have happened during the second 6 months of 2000 with the Human Genome Project (**HGP**), and related genomics news, provided chronologically**:**

July 2000. **Celera Genomics** (Rockville MD) offered a multi-year deal to academic centers for access to their growing database of the entire human genome. **Harvard University** announced its subscription, with financial terms undisclosed [*Nature* **406:** 229, 2000], making it the second academic center to sign up. **Vanderbilt University** (May 2000) was the first. **University of Cincinnati** was the fourth medical center to sign up.

The genetically isolated populations—such as those of Finland and Sardinia—may not be the panacea for linkage disequilibrium mapping of common disease genes that they have previously been

cracked up to be [*Nature Genet* **25:** 320, 2000].

Emphasis continues to increase on "functional genomics," the importance of elucidating gene function [*Nature Genet* **25:** 243, 2000]. Which reminds me of an October 99 Airlie House (Virginia) meeting at which a colleague said he'd been studying functional genomics for more than 30 years, ... "only, ... back in those days we called it 'biochemistry.' "

August 2000. Now that some of us have access to the Celera database, we are beginning to realize just how many "gaps of unknown distance" exist in the so-called "complete" human genome database. Leading to an editorial [*Nature Biotechnol* **18:** 803, 2000] which closed by saying, "Musicologists are now able to declare Schubert's Unfinished Symphony "essentially complete," arguing that the great composer did write down all the notes he intended to use, albeit not in precisely the right order (with some of the fiddly boring bits left to be filled in by others). ... The best news of all, of course, is that we can all go home at 4:37 p.m. in the afternoon after a full day's work."

For the HGP, first came humans, then mice and zebra fish (*Danio rerio*), and most recently rats [*Science* **289:** 1267, 2000]. Other requests for vertebrate genomes to be sequenced soon include the chimpanzee, gorilla, dog, chicken, and puffer fish (*Fugu rubripes*). Theoretically, the mouse and rat genome sequences will be completed at about the same time, since these two rodents are only 17 million years diverged from one another.

A Mouse ***Phenome*** Project, based at The Jackson Laboratory (Bar Harbor Maine), is being set up [*Mamm Genome* **11:** 715, 2000]. In order to fully exploit the power of rodent genetics, we need to develop a centralized database containing detailed information describing the **phenotypic** (each trait, e.g. white, or spotted, coat color; blood pressure; high learning ability, etc.) and genetic diversity among inbred mouse strains. An important practical difference between genome and phenome is that while the genome is limited to ~3 billion base pairs, the phenome is infinite—depending on how far we wish to go.

A great review on sequencing, sequencers, microarrays, and future trends appeared in two parts in *Genome Res* **10:** 1081, 1288, 2000].

The complete genome sequence of *Pseudomonas aeruginosa* (an opportunistic bacterium often found in very ill or debilitated patients) was reported to be 6.3 million base pairs and 5,570 putative genes [*Nature* **406:** 959, 2000]. This is the largest of all bacterial genomes to date and, in fact, approaches the number of 6,200 genes in the yeast genome.

In previous issues of ***Interface*** the importance of ***horizontal transfer*** (capture of one or more genes from one organism by a second organism) was emphasized. The completed genome sequence of *Vibrio cholerae* (the cause of cholera, a severe diarrhea) was found to have ~4 million base pairs encoding 3,885 potential genes and approximately ***one-fourth*** of its entire genome represents horizontal transfer of host-derived genes from an ancestral *Vibrio* species [*Nature* **406:** 477, 2000]**..!!**

September 2000. Plants are notorious for having a 1,000-fold variation in their genome sizes—ranging from 125 million bases in *Arabidopsis* (the tiny mustard) to 120 billion bases in *Fritillaria* (an ornamental lily) [*Science* **289:** 1455, 2000; *Genome Res* **10:** 893, 2000]. See "Gene number and Superiority?" article in this issue.

The completed genome of *Thermoplasma acidophilum* (a bacterium that grows at pH 2 and 59 °C) revealed 1.5 million bases and 1,509 putative genes [*Nature* **407:** 508, 2000]. And it looks like about 17% of its genes have been acquired via horizontal transfer.

The Japanese Institute of Physical and Chemical Research (RIKEN) held a Functional Annotation of Mouse (FANTOM) meeting in Tokyo of about 50 geneticists, biologists and bioinformaticists to annotate a subset of its library of 128,500 mouse cDNA clones from histologically and developmentally diverse tissues—purported to be the largest collection in the world [**http://www.riken.go-jp**].

The leaders of the international effort to sequence the human genome met in Paris to plot their strategy for "finishing" the human genome. Currently, "only 25% is in an assembled, accurate form" [*Nature* **407:** 122, 2000].

October 2000. The importance of the ***transcriptosome*** (a set of genes concomitantly expressed, subsequent to some common "inducing" signal) was reported in *Genome Res* **10:** 1431, 2000. These authors from RIKEN offer the ultimate in differential display and subtraction library techniques..!!

The status of many bacterial genome projects, and the importance of horizontal gene

transfer, was reviewed in *Nature Biotechnol* **18:** 1049, 2000.

Celera Genomics announced it had sequenced 95% of the mouse genome comprising three different strains, and that it plans to create a mouse SNP database that will include all results reported by the Mouse Sequencing Consortium.

The National Institute of General Medical Sciences (NIGMS) announced the launch of the Structural Genomics Initiative (SGI), the largest project to date to solve the 3-dimensional structure of 10,000 proteins—each representing a unique protein family [*Nature* **407:** 549, 2000].

November 2000. Now that the sequences of all the 19,099 genes in *Caenorhabditis elegans* (the small roundworm) are known, it is possible to systematically knock out each one, or combinations, and see what happens in the intact worm [*Nature* **408:** 325 & 331, 2000]. This is being done by RNA interference (RNAi), a technique that was discussed in an earlier issue of ***Interface***.

December 2000. The genomic sequence of the flowering tiny mustard plant, *Arabidopsis thaliana* (with 125 million bases in its genome) was reported [*Nature* **408:** 796, 816, & 820, 2000; *Science* **290:** 2105 & 2114, 2000]. A total of 25,498 genes encoding proteins from 11,000 families was found.

The "cooperation" that characterized the international HGP and the private company Celera (reported last June) is shifting again toward fierce competition as the projects' members vie to decipher the genetic codes of other species [*Nature* **408:** 758, 2000; *Science* **290:** 2042, 2000].

Ethical, Legal and Social Issues...

What follows is a synopsis of some of the more interesting things that have happened during the second 6 months of 2000 with ethical, legal and social issues (**ELSI**) related to the Human Genome Project, provided chronologically**:**

July 2000. Eaves and coworkers [*Nature Genet* **24:** 320, 2000] typed 21 short tandem repeats (STRs) across 6.5 centiMorgans of chromosome 18 on samples of 800 chromosomes from Sardinia, Finland, and the United States. The conclusion was that genetic isolates—such as the one deCODE is studying with the Icelandic population—are not significantly more valuable than mixed populations for disequilibrium mapping of common variants that might underly complex diseases. This report has created renewed debates on both sides of the issue [*Nature* **406:** 340, 2000]**..!!**

Concerning genetically modified (GM) plants/foods, the European Commission (EC) has developed a "proactive approach" whereby companies can anticipate legislative requirements that do not actually come into force for 2 or more years [*Nature Biotechnol* **18:** 705, 2000].

Contrary to a 1999 report in *Nature Biotechnology*, scientists at the University of Illinois in Urbana found no effects on butterfly health or mortality when exposed to *Bacillus thuringiensis* toxin (*Bt*)-containing transgenic corn pollen [*Proc Natl Acad Sci USA* **97:** 7700, 2000].

August 2000. Three "rational limits" on ***genomic patents*** were proposed [*Nature Biotechnol* **18:** 805, 2000]**:** [a] one should consider whether automated gene sequencing really "invents or discovers," within the meaning of patent laws**;** [b] from an economic perspective, a tool such as a single-nucleotide polymorphism (SNP) or expressed sequence tag (EST) should be patentable only if the benefit of such a patent (in strengthening incentives to develop genomic information) is greater than the costs of the patent in foreclosing others' abilities to use this information about the genome**;** [c] we need to reflect on what is a patentable invention versus what is an unpatentable piece of information, or a "law of nature."

Another independent study, simply looking at variation in a 360-bp fragment of mitochondrial DNA [*Nature Genet* **25:** 373, 2000], also questions the usefulness of a genetically isolated population such as those of Iceland or Sardinia. These data of Árnason and coworkers do not support the model of a recent genetic bottleneck and subsequent expansion corresponding to the colonization of Iceland 1,100 years ago. This study was vigorously challenged, however, in December [*Nature Genet* **26:** 395, 2000].

How are community protections related to individual informed consent? Is it more appropriate

to conceive of a community as a vulnerable group protected by current regulations? Might a community use added protections for research to legitimize the oppression of groups within the community? Who might be reasonably considered as the true "community leader?" What if the community wants to suppress adverse or undesirable research findings? These, and more, bioethical issues are discussed in an excellent forum [*Science* **289:** 1142, 2000].

Kansas returns to the 21st Century**..!!** Scientists, many new to any political activities, vigorously campaigned in voting districts this summer to help oust three anti-evolution members of the Kansas Board of Education, thereby clearing the way for evolution to once again be taught in the state's classrooms [*Nature* **406:** 552, 2000]. This about-face might help raise the "grade of F minus, disgraceful" for Kansas in an evaluation of all states' school systems and how they teach evolution [*Nature* **407:** 287, 2000].

Monsanto (St Louis, Missouri) announced royalty-free licenses to its technology for producing varieties of rice that contain enhanced levels of provitamin A [*Nature* **406:** 549, 2000]. Development of such transgenic rice has been detailed in previous issues of ***Interface***.

September 2000. Although a majority of U.S. citizens remains supportive of "biotechnology," fervent opposition to such issues as genetically modified (GM) crops is on the rise [*Nature Biotechnol* **18:** 939, 2000].

Legislation on human genome research was introduced in Estonia's Parliament. The Estonian Genome Project (EGP) proposes to create a database of health and genetic data from 70% of Estonia's 1.4 million people. Unlike the Icelandic population focused on disease common to Icelanders, the EGP proposes to elucidate genes involved in diseases prevalent throughout Europe—such as cancer and asthma [*Nature Biotechnol* **18:** 1135, 2000].

October 2000. Although the raging controversy continues over whether or not *Bt* corn affects nearby butterfly populations [*Nature Biotechnol* **18:** 1030, 2000]**:** "More than 28 million acres of North America were planted with *Bt* corn in 1999, approximately 40% more than in 1998, yet the monarch butterfly population flourished and increased by about 30%" (according to the environmental monitoring group, Monarch Watch).

November 2000. Massachusetts has voted to pass a law that prohibits genetic discrimination by employers and health insurance agents [discussed in *Nature Genet* **26:** 1, 2000]. In contrast to the Massachusetts law on insurance, genetic testing and privacy protection, the federal U.S. legislation addresses only the issue of discrimination, and even that in a narrow context. The Health Insurance Portability and Accountability (**HIPA**) prohibits insurers from using genetic information to discriminate against individuals in group insurance plans (which comprise ~95% of the population). There is nothing to prevent companies from requesting or requiring genetic information, using this information to set premiums of those who seek individual health insurance, or ruling against employers who base decisions on such genetic information.

The Japanese Fishery Agency is clamping down on the sale of illegal whale meat by archiving the DNA from captured whales. Eventually, a database would allow the meat in supermarkets to be traced [*Nature* **408:** 508, 2000].

Canavan disease affects one in 6,400 Ashkenazi Jewish children**;** the disease is fatal, with symptoms appearing 3 months after birth—due to a deficiency of the enzyme aspartoacylase which gradually destroys the central nervous system. A Canadian father with two affected children persuaded a Chicago scientist to identify the gene and design a genetic test (which he did). Now, the family is suing the researcher for "misappropriation of trade secrets." This is the first case in which tissue donors have taken researchers to court for control of a gene [*Science* **290:** 1062, 2000].

The can of worms surrounding genetic tests, and family members willing to take these tests, is discussed in *Nature Genet* **26:** 251, 2000.

December 2000. Previous issues of ***Interface*** have described the approach deCODE has taken to gain DNA from Icelanders. Further opposition to this now appears in *N Engl J Med* **343:** 1734, 2000. As one Icelander puts it that "the Icelandic Act is unworkable in a Western democracy because its very nature is totalitarian."

LETTERS TO THE EDITOR

RESPONSES/COMMENTS TO VARIOUS QUESTIONS

Q ***Now that we supposedly have the entire human genome sequenced, what is left for scientists to do?***

A Even with the full human sequence in hand, there are a few remaining things that we need to understand:

- *DNA sequence organization*
- *Chromosomal structure and organization*
- *Gene number, exact chromosomal locations, and functions*
- *Predicted, versus experimentally determined, gene function*
- *Gene regulation (tissue and cell-type specificity, how "gene batteries" and transcriptosomes are coordinately regulated)*
- *Coordination of gene expression with protein synthesis and post-translational controls*
- *Noncoding types of DNA, amount, distribution, information content, and functions (if any)*
- *Interaction of proteins in complex molecular machines*
- *Evolutionary conservation among organisms ("evolutionary genomics")*
- *Protein conservation (structure and function)*
- *Proteomes (total protein content and function) in organisms*
- *Correlations of DNA sequence variants (insertions, deletions and single-nucleotide polymorphisms [SNPs] in health and disease)*
- *Disease-susceptibility predictions based on DNA sequence variants*
- *Genes involved in complex traits and multigene diseases*
- *Developmental genetics and genomics*
- *Complex-systems biology, including microbial consortia useful for restoring the environment.*

COMMENT ***I enjoy each issue of your NewsLetter. I usually read it during airplane trips, and I always read it cover-to-cover. There are so many great ideas for new research directions, as well as keeping me updated on so many diverse gene-environment topics. Keep up the good work! Keep 'em coming..!***

Your NewsLetter is great. I am downloading some of the articles to read. Fascinating! Thanks for sharing.

Q ***Is the issue about electromagnetic fields and human cancer now "dead in the water?"***

A After several National Academy of Sciences panels (discussed in several previous issues of ***Interface***), it looks more and more like extremely-low-frequency electromagnetic fields (ELF-EMFs) have been proven not to be initiators of cancer (*i.e.* causing genotoxicity, mutations). However, a recent report [*Environ Health Perspect* **108:** 967, 2000] has focused on whether ELF-EMFs might cause tumor promotion or progression. Using mouse leukemia cells that differentiate into red blood cells in culture when treated with dimethylsulfoxide, Chen and coworkers started at a threshold dose of 20 milligauss and found that a 60-hertz ELF-EMF causes a dose-dependent decrease in differentiation and increases in telomerase activity and proliferation. So, the final answer about EMFs and cancer might still be up in the air.

Animal Cloning, ...

What follows is a brief synopsis of some of the more interesting things that have happened during the second 6 months of 2000, with regard to animal cloning and related topics, provided chronologically**:**

July 2000. The Jackson Laboratory and the University of California at Davis announced the establishment of "Jax West," a facility that will use animal health and genetic quality control programs modeled after those at the original Jackson Laboratory in Bar Harbor, Maine.

In mammals cloned from adult donor cells, mitochondrial DNA (mtDNA) is derived mainly from the recipient cytoplast, but such DNA heteroplasmy does not appear to impede normal development [*Nature Genet* **25:** 255, 2000].

August 2000. Use of transgenic pigs as a source of organs for transplant into humans [*Nature Biotechnol* **18:** 1144, 2000] might be dangerous because of "creating viral diseases in humans," says Ian Wilmut [*Nature* **406:** 663, 2000], leader of the team that originally cloned Dolly the sheep.

September 2000. Mice have been repeatedly cloned, between four and six generations, without any evidence of developmental problems or premature aging, by Ryuzo Yanagimachi and coworkers based in Honolulu, Hawaii [*Nature* **407:** 318, 2000].

November 2000. Advanced Cell Technology (Worcester, Massachusetts) reported that the first cloned animal from an endangered species (the gaur, a south Asian ox-like animal) was born to a surrogate cow. The nucleus of a skin cell from a dead male gaur had been fused with a cow egg cell from which the DNA had been removed. Unfortunately, the gaur died several weeks later, dampening hopes that other endangered species could be cloned and extinct species might be revived [*Nature* **407:** 666, 2000].

Although Dolly the cloned sheep showed evidence of premature aging (the telomeres of her chromosomes were like that of a 9-year-old sheep corresponding to the age of the donor nucleus, although Dolly was only 3 years old at the time), there appears to be no evidence of such premature aging in cloned cattle [*Nature Genet* **26:** 272, 2000].

ONLY DEAD FISH SWIM WITH THE CURRENT

"Life is 10% of what happens to you, and 90% of how you respond to it."

To steal ideas from one person is "plagiarism" - to steal from many is "research".

SCIENCE LITE

ASSMOSIS: The process by which some people seem to absorb success and advancement by kissing up to the boss rather than working hard

BLAMESTORMING: Sitting around in a group, discussing why a deadline was missed or a project failed, and who was responsible

CUBE FARM: An office filled with cubicles

GENERICA: Features of the American landscape that are exactly the same no matter where one is, such as fast food joints, strip malls, and subdivisions

IRRITAINMENT: Entertainment and media spectacles that are annoying, but you find yourself unable to stop watching them

MOUSE POTATO: The on-line, wired generation's answer to the couch potato

OHNOSECOND: That minuscule fraction of time in which you realize that you've just made a BIG, uncorrectable, mistake

PERCUSSIVE MAINTENANCE: The fine art of whacking the heck out of an electronic device to get it to work again

PRAIRIE DOGGING: When someone yells or drops something loudly in a cube farm, and people's heads pop up over the walls to see what's going on

SALMON DAY: The experience of spending an entire day swimming up stream only to get screwed and die in the end

SEAGULL MANAGER: A manager who flies in, makes a lot of noise, poops on everything, and leaves

SITCOMs: (Single Income, Two (or Three) Children, Oppressive Mortgage). What yuppies turn into when they have children and one of them stops working to stay home with the kids

STARTER MARRIAGE: A short-lived first marriage that ends in divorce with no kids, no property and no regrets

STRESS PUPPY: A person who seems to thrive on being stressed out and whiny

SWIPED OUT: An ATM or credit card that has been rendered useless because the magnetic strip is worn away from extensive use

VULCAN NERVE PINCH: The taxing hand position required to reach all the appropriate keys for certain commands. For instance, the arm reboot for the Mac II computer involves simultaneously pressing the Control Key, Command Key, the Return Key, and the Power On Key.

WOOFs: Well Off Older Folks

XEROX SUBSIDY: Euphemism for swiping free photocopies from one's workplace

YUPPIE FOOD STAMPS: The ubiquitous $20 bills spewed out of ATMs everywhere. Often used when trying to split the bill after a meal, each owe $8, but all anybody's got are yuppie food stamps"

Human Gene Variability,...

What follows is a synopsis of some of the more interesting findings reported during the second 6 months of 2000, concerning our realization of how variable the human genome is and related topics, provided chronologically**:**

July 2000. There has been an ongoing debate as to how the Polynesian islands were populated, 4,000 to 5,000 years before the present, by peoples from Southeast Asia. Looking at the Y chromosome patterns of 551 males from 36 populations living in Southeast Asia [*Proc Natl Acad Sci USA* **97:** 8225, 2000], **Ranjan Deka** and coworkers found evidence for two independent migrations—one toward Taiwan and a second toward Polynesia through Southeast Asia.

One's **haplotype** is the string of DNA variants (usually referring to a specific gene) that resides on one chromosome, *i.e.* is this gene from the mother or the father? Haplotyping is difficult because each cell contains two copies of each gene (one on each chromosome). A recently proposed nanotube-based atomic force microscope (AFM) technique [*Nature Biotechnol* **18:** 760, 2000] may soon allow researchers to observe DNA sequence variants on a chromosome directly.

Orchid Biosciences (Princeton, New Jersey) announced a deal to score the prevalence of 60,000 single-nucleotide polymorphisms (SNPs) identified by the SNP Consortium.

September 2000. The importance of analyzing SNPs (at distances of ~30,000 bases throughout the genome) in helping to unravel complex genetic traits and diseases was reviewed [*Human Mol Genet* **9:** 2403, 2000]. A SNP map of human chromosome 22 [*Nature* **407:** 516, 2000] and how to create a dense map of 30 to 500 thousand SNPs to scan the human genome [*Nature* **407:** 513, 2000] have been described, but this approach might be far too simplistic than what some expect [*Nature Genet* **26:** 151, 2000].

The summary of a "Genetic History of Modern Humans" May 24-26 2000 meeting in Paris [*Trends Genet* **16:** 381, 2000] underscores the theme of the leading article of our issue #19 of ***Interface:*** that "racial grouping is a myth."

September 2000. How fast do new species develop? A genome with 15,000 genes could acquire between 60 and 600 duplicate genes over a million years [*Science* **290:** 1065, 2000].

Using Y chromosome sequence variation, Underhill and coworkers conclude that anatomically modern humans left Africa between 35,000 and 89,000 years ago [*Nature Genet* **26:** 358, 2000].

December 2000. Using mitochondrial genome mutation analysis, Ingman and coworkers suggest that modern humans left Africa between 52,000 and 172,000 years ago [*Nature* **408:** 708, 2000].

What Alternatives Does a Gene Have?

Although it now appears that humans have only about 31,000 genes, scientists are postulating there might still be several hundred thousand proteins produced from this small number of genes. How might this occur? After transcription of the DNA into nuclear RNA (nRNA), ***posttranscriptional*** modifications occur—including messenger RNA (mRNA) formation by spliceosomes. mRNA can be alternatively spliced, depending on "splice sites" in the nRNA transcript. mRNA then is translated into protein on ribosomes in the cytoplasm, and proteins can undergo many ***posttranslational*** modifications including phosphorylation, glycosylation and ubiquitination.

A gene which appears to hold the world record so far, for alternative splicing, is the fruit fly homolog of the Down syndrome cell adhesion molecule (*DSCAM* gene), which maps to human chromosome 21 [*Cell* **101:** 671, 2000]. The spliceosome makes innumerable choices when it comes to exons 4, 6 and 9—for which there are 4, 48 and 33 alternative mRNAs, respectively**..!!** If each exon that slots into any one position is capable of independent splicing with regard to all exons variably spliced into other slots, then the *DSCAM* gene could generate more than 38,000 variant mRNAs. How many of these actually form proteins is not yet known.

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Observations by a Biologist

Water, water everywhere and many drops to drink

We all know that water is important but did you know the following?

75% of Americans are chronically dehydrated (and so is at least half the world's population).

In 37% of Americans, the thirst mechanism is so weak that it is often mistaken for hunger.

Even MILD dehydration will slow down one's metabolism as much as 3%.

One glass of water was found to shut down midnight hunger pangs for almost 100% of the dieters examined in a University of Washington study.

Lack of water is the #1 trigger of daytime fatigue.

Preliminary research indicates that 8-10 glasses of water a day could significantly ease back and joint pain for up to 80% of sufferers.

A mere 2% drop in body water can trigger fuzzy short-term memory, trouble with basic math, and difficulty focusing on the computer screen or on a printed page.

Drinking 5 glasses of water daily decreases the risk of colon cancer by 45%, plus it can slash the risk of breast cancer by 79%, and bladder cancer by 50%.

Are you drinking the amount of water you should every day?

(*FROM THE INTERNET*)