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INTERFACE:
GENES AND THE ENVIRONMENT

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Ethical Issues and Genetic Research

Genes determine the characteristics for all life forms. As with all other species, we humans are a part of a heterogeneous population. These differences at each genetic locus--called polymorphisms--contribute to our "visible," as well as "invisible," characteristics. "***Phenotype***, or ***trait***," is defined as the outward characteristics resulting from the interaction between our genes and our environment. "***Genotype***" is defined as the actual DNA characteristics that make up each trait.

That "phenotype" has been used as a basis of social choice is literally as old as Life itself. The use of phenotype (and, therefore, genotype) for discrimination is an ancient yet contemporary issue. Being aware of phenotype is old in the sense that the visible manifestations of our genetic makeup have always been used for selection in all aspects of living--including the search for mates, the avoidance of adversaries, participation in social stratification, social acceptance as well as ridicule, gender-related genocide and infantocide, ethnic cleansing, and innumerable other behaviors. These ancient conflicts stemmed mainly from ***cultural***, ***territorial***, ***monetary***, and ***religious*** differences.

IN THIS ISSUE

The Human Genome Project

Now, because of the explosion in molecular biology and genetics these past two decades and the Human Genome Project since October 1990, the genetic differences that we all harbor, in addition to those that are overtly expressed as a phenotype, can be determined with incredible precision. The Human Genome Project is a world-wide collective research effort, which is aimed at mapping and sequencing the entire 3 billion base pairs (DNA) of the human genome, at a cost of about $3 billion over 15 years. It is possibly the most important scientific undertaking in the last half of this century, and has the potential for enormous benefit for mankind. The impact of this project will be felt in many areas--such as reproductive planning, prenatal diagnosis and treatment, preventive health, and therapeutic intervention. The elucidation of our genetic makeup, identifying each of our 50 to 100 thousand genes, should provide us with the opportunity to advance the quality of life for millions of individuals. More often than not, however, knowledge of this magnitude is met with fear and apprehension. The basis for these worries remains ***cultural***, ***territorial***, ***monetary***, and ***religious***.

Apprehensions

Concerns have arisen about the impact of the Human Genome Project on society. Will the mapping of the human genome provide information that might be used somehow to define individuals as "uninsurable," "unemployable," "high risk," "marginally intelligent," or "sociopathologic"--solely by virtue of their genetic makeup? Is there reason for apprehension? History would say yes.

It has taken tens of thousands of years of social evolution for *Homo sapiens* to develop a collective

consciousness that begins to recognize that the use of phenotype (gender, color and other anatomical characteristics) to create inequities in human rights--has serious negative social consequences. Great strides have been advanced in the last 200 years, beginning with the concept of equality (under the law) for individuals with all varieties of genetic makeup. Largely due to the untiring activities of the African-Americans in this country, equality under the law for racial minorities has been advanced. This also includes protection of women, who in many cultures have been the subjects of gender-related discrimination.

Ethical, legal and social issues (ELSI)

A portion (3%) of the budget for the Human Genome Project has been dedicated to ethical, legal and social issues, which are recognized as an important concern, and are being addressed at the same time as the science proceeds with mapping and sequencing of the DNA. The activities of the Human Genome Project and other scientific inquiries into the human genome are moving so rapidly that the legal system will have to contend with numerous novel cases. Conferences are being held--aimed at deciding how to use genetic information in criminal and civil cases. Just such a workshop, sponsored by the ELSI component of the Department of Energy (DOE) Human Genome Program, was held in July 1996 for a group of judges and science advisors. The apprehensions are great--concerning the possibility that genetic makeup will create a class of unemployable and/or uninsurable people.

On the other hand, the efficacy of using DNA data in court as evidence is valuable, especially since experts have pointed out that it is far superior to eyewitness accounts (which have been described as having only 50:50 odds for accuracy).

Employees, employers and health insurance

It is a fact that employers already often discriminate on the basis of genetics--using "appearance" or obvious phenotypes, such as gender, stature and color. When queried about the use of genotype as a point of discrimination, 330 companies of the Fortune 500 responded to the questionnaire. Of these 330, only 12 indicated that they used biochemical genetic screening, and they did not anticipate using direct DNA screening in the next 5 years. This may be reassuring**;** however, if a simple cheap test were to become available next year, would it be used? If the company knew that an employee would cost thousands of dollars in pay-outs for an easily detectable preexisting condition, would they hire that applicant? In fact, would they retain a current employee if they were to learn about such a condition? Surveys indicate that 42% of companies considered a job applicant's "health insurance risks" as an important factor in determining employability.

The ever-rising cost of employee health insurance is also reinforcing our anxieties. In 1965 only 8% of pretax company profit was spent on health care costs**;** however, by 1989 that figure had escalated to a whopping 56%. Companies have tried to restrict employment of smokers, high-cost users of health care, HIV-positive individuals, and others. Health-care insurance companies classify many common conditions as "higher premium," "exclusion waiver," or "denial" (**Table 1**). In addition, there are issues of a right-to-privacy during adoption proceedings and child custody decisions.

Discrimination on the basis of genetic traits is, in fact, a clear violation of Title VII of the Civil Rights Act of 1964, since these very often fall along racial, ethnic and gender lines. Nonetheless, a classic example of genetic information being used for discrimination occurred in the 1970s--when sickle cell trait as well as sickle cell anemia were used as criteria for denying employment in a wide range of jobs. Laws were enacted in Florida, Louisiana, and North Carolina in an attempt to stop this bias. These were the first laws that directly confronted genetic discrimination in the workplace. States that followed this lead with legislation included New Jersey (protecting individuals with several blood disorders**;** 1981), and Oregon (prohibiting employers from requiring applicants to undergo "genetic screening"**;** 1989). New York (1990) and Wisconsin (1992) soon followed suit.

American Disabilities Act (ADA)

The ADA was signed into law by President Bush (1990), with these words**:** "...this act is powerful in its simplicity. It will ensure that people with disabilities are given the basic guarantees for which they have worked so long and so hard ...(for)... independence, freedom of choice, control of their lives, and

Table 1. RISK CLASSIFICATION BY COMMERCIAL HEALTH INSURERS: COMMON CONDITIONS REQUIRING A HIGHER PREMIUM, EXCLUSION WAIVER, OR DENIAL

HIGHER PREMIUM	EXCLUSION WAIVER	DENIAL
allergies	cataract	AIDS
asthma	gallstones	ulcerative colitis
back strain	fibroid tumor (uterus)	liver cirrhosis
hypertension (controlled)	hernia (hiatal/inguinal)	diabetes mellitus
arthritis	migraine headaches	leukemia
gout	pelvic inflammatory disease	schizophrenia
glaucoma	chronic otitis media (recent)	hypertension (uncontrolled)
obesity	spine/back disorders	emphysema
psychoneurosis (mild)	hemorrhoids	stroke
kidney stones	knee impairment	obesity (severe)
emphysema (mild to moderate)	asthma	angina (severe)
alcoholism/drug use	allergies	coronary artery disease
heart murmur	varicose veins	epilepsy
peptic ulcer	sinusitis (chronic or severe)	lupus erythematosus
colitis	fractures	alcoholism/drug abuse

Taken from "Office of Technology Assessment, U.S. Congress, Medical Testing and Health Insurance 60" (1988) (Table 2-5)

the opportunity to blend fully and ***equally*** into the right mosaic of the American mainstream." According to Mark Rothstein, Professor of Law and Director of the Health Law and Policy Institute at the University of Houston Law Center, the ADA was a "monumental piece of civil rights legislation." This Act "limits the scope of preemployment and ... medical inquiries, protects the confidentiality of health records, ... and requires (employer) accommodations to permit qualified individuals with disabilities to gain access to the American work force."

However, the ADA is not perfect, since it does not inhibit employers from exclusionary practices regarding health insurance and services for the disabled [see also on page 9 of this issue: "***Intriguing Ethical Questions***"]. From the ADA are excluded**:** those with behaviorial disorders, homosexuality and bisexuality, those with "listed" diseases (including carriers of six pathogens transmitted by infected food handlers), and illegal drug and alcohol users. The ADA was initially enacted without consideration of individuals having various genetic conditions, but the venue for interpretation is certainly present. According to the Equal Employment Opportunity Commission's definition of "disability," an X-linked genetic disorder is named, and therefore genetic diseases may coincidentally be included in the ADA's definition of disability. The ADA covers mental and physical impairments that "substantially limit" important activities in our lives. Not covered are characteristics that are less critical--such as weight, hair color, handedness, chronic lateness, varicose veins, poor judgment, small stature, etc. The extent to which the ADA protects those with genetic conditions remains to be tested in court.

President Clinton signed into law "The Health Insurance Portability and Accountability Act of 1996," which is designed to protect individuals from the use of genetic information to deny insurance coverages when moving from one job to another. This law also has not yet been tested in court.

Genetic privacy

Scientists have only begun to comprehend the degree of similarity (which dwarfs any differences) in our genetic makeup. It has been estimated that as little 0.1 % of our genome can be responsible for our differences. In view of the fact that the problem associated with genetic discrimination is not new, but has only taken on a new face, one would anticipate that immediate steps need to be taken to ensure that current laws will be modified to provide equitable protection for all. This action will require an educated public, as well as ample healthy debates of these policy issues.

Conferences have been held by the AAAS (American Association for the Advancement of Science) that deal with the economic, social and psychological effects of genetic testing and disclosure. The main concerns are **[a]** that there will be no beneficial intervention for those who are identified as "at risk," **[b]** that there is very little in the way of training provided for health personnel to counsel individuals about genetic tests, and, very importantly, **[c]** that such medical information still has the potential to be used as a means to discriminate and deny insurance and employment.

Genetics, ethics and the patient

Other concerns center around issues of disclosure and consent--involving research on the human genome. A recent article on disclosure and informed consent has just appeared [*Nature Genet* **15,** 16-20 (Jan 1997)]. Consent needs to reflect a rational choice by the patient in a situation that is probably not beneficial to him/her. There is also a duty of the investigator to alert the subject to dangers--such as stress, anxiety, and the impact on the ability of one to obtain health insurance. The Office of Protection from Research Risks (at the National Institutes of Health, Bethesda, Maryland) formulated a document in 1993 aimed at educating scientists about disclosure in genetic research, entitled "***Protecting human research subjects: Institutional Review Board guidebook***." This has spurred many IRB committees in the nation (including ours at the University of Cincinnati) to rewrite their consent forms specifically to include wording relevant to genetic research and tests.

Some issues that should be in the scope of consent forms include**: (1)** a clear description of the role of the subjects, **(2)** identification of all members of the research team, **(3)** plans for protecting confidentiality, **(4)** plans for archiving the subject's DNA or cell lines, and **(5)** how the subject's DNA should be distributed. The consent forms should also include**: (6)** disclaimers noting that the analysis of each DNA sample may contribute to product development, in which the patient would share no benefits, and **(7)** warnings that the subject may discover sensitive genetic information (*e.g.* paternity) which might have harmful effects if disseminated. The subject needs also to be informed that **(8)** the findings could indicate that he/she has a trait for a serious illness (*e.g.* likelihood of developing early-onset Alzheimer's disease) which might increase difficulties in obtaining insurance coverage. Once the information is known to the patient, disclosure of this information may be required later in answering questions during insurance examinations. Research aimed at discovering genetic profiles and disease status should be conducted only on those subjects who are willing to accept these risks.

The future will be exciting

In summary, what is already known about our genes from The Human Genome Project represents just the tip of the iceberg. The next 5-10 years are going to become incredibly complicated--from the standpoint of ethical, legal and social issues surrounding the interactions of our genes with our environment.***----Contributed by Eula Bingham, Marian Miller and Dan Nebert***

Environmental Genome Project

In early March 1997 **Ken Olden** (Director, National Institute of Environmental Health Sciences; NIEHS) introduced to Congress his vision of an "Environmental Genome Project." This new program was proposed to fund studies on identifying and characterizing human differences in at least 200 "critical genes" believed to play important roles in disease caused by environmental agents. The total cost may exceed $60 million over several years.

The plan would be to collect DNA from 1,000 people derived from major ethnic groups and to sequence these "susceptibility" genes, looking for allelic differences (so-called "genetic polymorphisms") responsible for variability in toxic responses. This approach is very similar to the theme of our Center for Environmental Genetics (**CEG**) at the University of Cincinnati. Olden hopes to launch the project in 1998 with $10 million or more.

SCIENCE LITE

TWENTY WORDS (listed alphabetically) THAT SHOULD EXIST

1. **ACCORDIONATED** (ah kor' de on ay tid) *adj* Being able to drive and refold a road map at the same time.

2. **AQUADEXTROUS** (ak wa deks' trus) *adj* Possessing the ability to turn the bathtub faucet on and off with your toes.

3. **AQUALIBRIUM** (ak wa lib' re um) *n* The point where the stream of drinking fountain water is at its perfect height, thus relieving the drinker from (a) having to suck the nozzle, or (b) squirting her(him)self in the eye (or nose or ear).

4. **BURGACIDE** (burg' uh side) *n* When a hamburger can't take any more torture and hurls itself through the grill into the coals.

5. **BUZZACKS** (buz' aks) *n* People in phone marts who walk around picking up display phones and listening for dial tones--even when they know the phones are not connected.

6. **CARPERPETUATION** (kar' pur pet u a shun) *n* The act, when vacuuming, of running over a string or a piece of lint at least a dozen times, reaching over and picking it up, examining it, then putting it back down to give the vacuum one more chance.

7. **DIMP** (dimp) *n* A person who insults you in a cheap department store by asking, "Do you work here?"

8. **DISCONFECT** (dis kon fekt') *v* To sterilize the piece of candy you dropped on the floor by blowing on it, somehow assuming this will "remove" all the germs.

9. **ECNALUBMA** (ek na lub' ma) *n* A rescue vehicle that can only be seen in the rear view mirror.

10. **EIFFELITES** (eye' ful eyetz) *n* Tall, stringy people sitting in front of you at the movies who, no matter in which direction you lean, follow suit.

11. **ELBONICS** (el bon' iks) *n* The actions of two people maneuvering for one armrest in a movie theater or airplane.

12. **ELEVACCELERATION** (el' uh vax sel er ay' shun) *n* The mistaken notion that the more times you press an elevator button, the faster it will arrive.

13. **FRUST** (frust) *n* The small line of debris that refuses to be swept onto the dust pan and keeps backing a person across the room until he finally decides to give up and sweep it under the rug.

14. **LACTOMANGULATION** (lak' to man gyu lay' shun) *n* Manhandling the "***Open Here***" spout on a milk container so badly that one has to resort to the "illegal" side.

15. **NEONPHANCY** (ne on' fan see) *n* A fluorescent light bulb struggling to come to life.

16. **PEPPIER** (pehp ee ay') *n* The waiter at a fancy restaurant whose sole purpose in Life seems to be walking around, asking diners if they want ground pepper.

17. **PETROPHOBIC** (pet ro fob' ik) *adj* One who is embarrassed to undress in front of any household pet.

18. **PHONESIA** (fo nee' zhuh) *n* The affliction of dialing a phone number and then forgetting whom you were calling just as they answer.

19. **PUPCOUS** (pup' kus) *n* The moist residue left on a window after a dog has been pressing its nose to it.

20. **TELECRASTINATION** (tel e kras tin ay' shun) *n* The act of always letting the phone ring at least twice before you pick it up, even when you know who is calling.

CEG-SPONSORED SPEAKERS

Ranjan Deka, PhD
Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, PA
December 16, 1996 ***"The unstable genome: dynamic mutations and evaluation of repeats with special reference to myotonic dystrophy."***

Distinguished Lecturer
Samuel H. Wilson, MD
Deputy Director NIEHS, Research Triangle Park, NC
February 26, 1997 ***" Perspective on new approaches in environmental health research"***
and ***"DNA polymerase beta in mammalian base excision repair."***

Nathaniel Rothman, MD, MPH, MHS
Senior Clinical Investigator
National Cancer Institute, Bethesda, MD
March 13, 1997 ***"The study of genetic susceptibility of occupational and environmental diseases."***

Mark A. Rothstein, JD
Professor and Director of the Health Law and Policy Institute, University of Houston Law Center, Houston, TX
March 26, 1997 ***"Genetic privacy."***

CEG Members in the News

Eula Bingham was a panelist at a Workshop entitled "Ethical Considerations in Nuclear Workers" in February 1997 (Oakridge, Tennessee).

Tom Doetschman delivered two talks entitled ***"Nonoverlapping phenotypes of the three TGFβ knockout mice"*** and ***"TGFβ signaling in development and cell cycle"*** at a symposium on "Transgenic Technologies in Analysis of Developmental Mechanisms" in February 1997 (Helsinki, Finland**).** In February 1997, he also delivered a seminar on ***"FGF2 function as assessed by transgenic and knockout mice"*** at the Institute of Molecular and Cell Biology, National University of Singapore, (Malaysia).

Sohaib Khan presented two seminars in February 1997: ***"Understanding estrogen receptor function through protein-protein interactions: Implications in breast cancer"*** at the Lawrence Berkeley National Laboratory (Berkeley, California) and ***"Mechanism of estrogen receptor action"*** at HELIOS Pharmaceuticals (Louisville, Kentucky).

Grace Lemasters was appointed Director of the Division of Epidemiology and Biostatistics in the Department of Environmental Health at the University of Cincinnati, and also to the editorial board of the Occupational and Environmental Medicine Journal. She presented a lecture entitled ***"Cytogenetic effects of low level solvent, fuel and benzene exposure on aircraft maintenance personnel"*** in December 1996 (Hill Air Force Base, Utah).

George Leikauf presented an invited lecture entitled ***"Acute lung injury: genetic determinants and transgenic models"*** at a conference on the "Relationships Between Respiratory Diseases and Exposure to Air Pollution" in February 1997 (Hannover, Germany). He also delivered a talk entitled ***"Genetic determinants of asthma"*** at the Imperial College of Science, Technology and Medicine, in March 1997 (London, United Kingdom). He presented an invited lecture at Research Triangle Park entitled ***"Surfactant deficiency and air pollution susceptibility"*** in March 1997 at a workshop on "The Use of Transgenic Model Systems in Molecular Toxicology."

Francis McCormack received a UC Challenge Grant for a proposal entitled "Molecular mechanisms of emphysema", and a Merit Award from the VA Hospital entitled "Structure function relationships of surfactant protein A in transgenic mice."

Dan Nebert, while enjoying a 3-month mini-sabbatical, gave a talk entitled ***"Genetic determinants of susceptibility to lung toxicity and cancer"*** at the Symposium on "Genetic Determinants of Susceptibility to Inhaled Pollutants," and a talk entitled ***"Possible role of the [Ah] gene battery in apoptosis"*** at the Symposium on "Perturbation of the Mitosis/Apoptosis Balance: A Fundamental Mechanism in Toxicology," during the 17th Annual Meeting of the Society of Toxicology in March 1997 (Cincinnati, Ohio). He also gave the lead-off talk entitled ***"Overview:generation of conventional and inducible knockout and other transgenic mouse lines"*** at the Workshop on "Use of Transgenic Model Systems in Molecular Toxicology," at the National Institute of Environmental Health Sciences (NIEHS) in March 1997 (Research Triangle Park, North Carolina)

Howard Shertzer presented an invited lecture entitled ***"TCDD- induced intracellular signaling pathways"*** at the Midwest Society of Toxicology in March 1997 (Indianapolis, Indiana).

Peter Stambrook presented a lecture entitled ***"New opportunities for development of transgenic model systems"*** as closing remarks at the conference on "The Use of Transgenic Model Systems in Molecular Toxicology," March 1997 at NIEHS (Research Triangle Park, North Carolina).

Jeff Whitsett delivered a talk on ***"Molecular and genetic control of pulmonary surfactant homeostasis: from genes to bedside"*** at the Rockefeller University in January 1997 (New York, New York) and in February 1997 he delivered a talk entitled ***"Gene transfer for therapy of genetic lung diseases"*** at Massachusetts General Hospital (Boston, Massachusetts).

LETTERS TO THE EDITOR

RESPONSES/COMMENTS TO VARIOUS QUESTIONS

COMMENT **Your *Interface* issue #9 with the article on "Oberschlesien" reminded me about the time we were traveling in Poland in the 'eighties. Upper Silesia was always a nightmare. This May my wife and I will travel to Krakow and therefore will pass through this area again. Let's wait and see if there are any detectable improvements in this very heavily polluted industrial region. ---*A reader from Jena, Germany***

Q **In your issue #8 you mentioned the 1996 work of McLachlan and coworkers about "environmental estrogens--in combination--being 160 to 1600 times more potent." I understand that there are now some questions about this "synergistic effect?"**

A *Yes, Ramamoorthy and coworkers from Texas A & M University and Research Triangle Park, North Carolina [Science **275,** 405 (Jan 1997)] find additive rather than synergistic effects. The results of Ashby and colleagues from Zeneca Central Toxicology Laboratory and Brunel University in England [Nature **385,** 494 (Feb 1997)] also do not support the assertion that synergism between environmental estrogens is likely to present a major human or wildlife health concern.*

COMMENT **In a group of 54 male breast cancer patients, about one third were found to have first-degree or second-degree female relatives with breast cancer [*Am J Hum Genet* 60, 313 (Feb 1997)]. These data suggest that some genetic factors predispose to breast cancer in both men and women; in fact, two men in this study had mutations in their *BRCA2* gene.**

It is worth noting that there has been a plea [*Nature Genet* 14, 235-236 (Nov 1996)] that we stop calling everything "THE gene for (name of any disease)" and begin to realize that virtually every disease and every trait (phenotype) is the result of the complex interaction of numerous primary genes and modifier genes--as well as the environment!

Several studies suggest that as many as four or ten genes other than *BRCA1* and *BRCA2* are responsible for increased risk of breast cancer. A recent candidate, *TSG101* mapped to chromosome 11, has been found to exhibit mutations in breast cancer [*Cell* 88, 143-154 (Jan 1997)].

The function of *BRCA1* remains elusive. The finding of a lack of transcriptional activation in four different *BRCA1* mutations in families predisposed to breast and ovarian cancer, compared with finding transcriptional activation in the unmutated normal gene [*Nature* 382, 678-679 (Aug 1996)] suggests that transactivation (and therefore the BRCA1 protein binding to DNA and regulating a set of genes) might be a true function.

Another exciting development concerns the BRCA1-associated RING domain (BARD1) protein [Nature Genet 14, 430 (Dec 1996)]. The normal BARD1/BRCA1 (protein-binding complex) interaction does not occur when BRCA1 proteins having the missense mutations that segregate with breast cancer susceptibility are used instead of the normal BRCA1 protein--indicating that BARD1 might be involved in mediating tumor suppression by BRCA1. Further evidence that BRCA1 is involved in transcriptional activation!

Q **At a conference for science writers sponsored by the American Cancer Society in Reston, Virginia, March 1997, a group at the University of Southern California reported that an abnormal allele (*A2*) of the human *CYP17* gene appears to be correlated with a 2-fold increased risk of breast cancer. How might you explain the contribution of this gene to breast cancer?**

A *The researchers showed preliminary evidence that women who get at least one copy of the **A2** allele produce more estradiol, begin menstrual*

*period at a young age, and have an increased risk of breast cancer that metastasizes earlier. The **CYP17** gene encodes a 17α -hydroxylase that is pivotal in taking steroids from pregnenolone and progesterone to androgens, then CYP19 (aromatase) takes androgens on to estrogens. It is possible that increased activity of the **CYP17** gene "moves the steroids more rapidly" to estrogens as the end-point--but further research will be needed to confirm this.*

*Congenital adrenal hyperplasia (CAH) can be caused by **CYP17** deficiency (as can three other P450 genes: **CYP11B1**, **11B2**, and **CYP21**--the latter being by far the most common cause). Affected individuals exhibit "low renin" hypertension--due to the accumulation of 17-deoxysteroids including aldosterone. Affected males present as phenotypically female with sexual infantilism.*

Q Okay, so a lab in England has now cloned a sheep, named "Dolly!" Do you wish to comment on this touchy subject of "cloning humans" in your NewsLetter?

A *Cells were cultured from the udder of a 6-year-old ewe. Although their cell cultures contained more than 90% mammary epithelial cells, Ian Wilmut and coworkers [Nature **385,** 810-813 (Feb 1997)] admit they cannot be certain that the DNA they cloned did not originate from a myoepithelial cell, fibroblast, or relatively undifferentiated stem cell. By starving the cells, they were able to achieve growth arrest, or "**G_0**" phase, in which the cells exit the growth phase--which causes changes in chromatin structure that appear to facilitate reprogramming of gene expression (and also decreases the incidence of chromosomal abnormalities). It is this regimen of **growth arrest** that appears to have made the donor nucleus more compatible with the cytoplasm of the recipient oocyte.*

*One of these cells from the 6-year-old ewe was then fused (via electrical shock) with an oocyte from which its original nucleus had been removed. This fusion, resulting in the 6-year-old nucleus interacting with the oocyte cytoplasm, then proceeded like a fertilized egg--undergoing cell divisions (the 2-cell, 4-cell, etc. stages). Six days later, the dividing cell mass (embryo) was placed into the uterus of a pseudopregnant ewe and raised to term. It should be emphasized that Dolly was the result of **277 fusions** involving presumably adult cells, and that the longevity and fertility of Dolly are not yet known. The biggest scientific breakthrough of these experiments is that **[a]** a cell's identity has been changed by reprogramming its genes and **[b]** differentiation has been proven not to be an irreversible process (although, with cancer, it is clear that a differentiated cell can return to embryonic-like dedifferentiated cells).*

*In 1952 an embryonic cell was cloned into a live frog. Experiments were repeated with an adult intestinal epithelial cell some 11 years later, and they got as far as producing normal-appearing tadpoles. This concept was the basis of Michael Crichton's book, "**Jurassic Park**," in which "dinosaur DNA was cloned in frog oocytes. The amazing result of Wilmut and coworkers is that an (apparently) **adult** cell was cloned to make another individual--in **mammals**. The first thing that needs to be done is to have another laboratory corroborate these results. Two monkeys, cloned from embryonic cells by Don Wolf and coworkers at the Oregon Regional Primate Research Center (Beaverton), were reported about a week after the sheep cloning study was reported--confirming that what had been done in frogs 45 years ago now appears to have been repeated in mammals.*

*What are the benefits of **cloning mammals**? We should be able to learn more about what turns genes on and off during development. Such cloning should lead to the production of animal models for studying human diseases--where **genetic homogeneity** exists in each animal; this now exists (to a great extent) in any inbred strain of mouse, but most other laboratory animals are quite genetically heterogeneous (especially cattle, sheep, dogs), which causes a lot of "background noise" in scientific experiments. Cloning particularly large or healthy cattle, pigs, etc. for the enhanced production of meat, cheese and milk might be extremely beneficial to starving world populations. Cloning animals having high levels of therapeutic compounds (drugs, antibodies, human insulin and other peptides, etc.) in their milk (or blood) will be very helpful to medicine. As Harold Varmus*

(Director of NIH) stated,"There is a whole gamut of possibilities in medicine."

*The ethical issues of **cloning humans** might be appropriate to mention--especially in this issue where "ethics" is the lead article. The "knee-jerk" reaction by the U.S. Government immediately to "call a moratorium on cloning for 3 months" has been met with considerable criticism by other countries. Basically, you can delay or outlaw a technique, but you cannot reverse the biology that has already been proven. The prevention of federally funded research, and a "recommended ban on cloning by private research companies," will not prevent such experiments from proceeding--especially if money and profits are involved. One need only be reminded of the biotech company that marketed last November the test for **BRCA1** and **BRCA2** sequencing. Because such tests might be positive but the patient does not develop breast or ovarian cancer, or negative but the patient does develop cancer, various agencies including the American Society of Human Genetics were strongly opposed to marketing such a test [discussed in issues #8 and #9 of **Interface**]. Yet, the test **was** put on the market and some women are running to their physicians, asking that they be tested.*

Intriguing Ethical Questions

During Mark Rothstein's recent lecture, entitled "Genetic privacy," the following legal cases were discussed. Several of the cases are listed here, because they are such excellent examples of what can happen (and is happening) in the fields of human genetics, environmental toxicology and forensic medicine.

Case #1: The patient is diagnosed with thyroid medullary cancer and dies within 2 years. Her eldest daughter develops the same disease 3 years later and 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: The patient is diagnosed with adenomatous polyposis coli (***APC;*** multiple tumors of the colon) in 1958 and is 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 is sometimes obligatory for the physician to relay 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 badly in a serious 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's disease--meaning that the patient has a 50% chance of developing this dominant disease that, on average, affects people by age 50. If she carries the ***HD*** 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 ***HD*** carrier (as is true of almost 90% of all children who have a parent diagnosed with Huntington's 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 ***HD*** allele. Although her side of the family has no Huntington's disease, her husband's father has died from this. This means that her husband has a 50% risk of carrying the ***HD*** 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 she had had a spontaneous miscarriage.

- What is the physician to do? What should the medical counselor do? If the medical or paramedical person arees to join in the practice of deceit early on, can you imagine the possible scenarios later?

Genomic Scanners, Like in a Grocery Store!

Eric Lander, Director of the Center for Genome Research at the Whitehead Institute (Cambridge, MA) and Chair of the External Advisory Committee of the Human Genome Project, predicts that a "genotyping chip" may one day be used to scan quickly an entire genome at a single pass. ***Affymetrix scientists*** (Santa Clara, CA) have already completed a 2-cm by 2-cm chip containing more than 100,000 different DNA sequences, each precisely placed (similar to a computer chip). This array can provide an efficient means of screening a DNA sample for the presence of small stretches that differ in only one base. Such differences--termed single nucleotide polymorphisms (SNPs)--are the same as "spelling mistakes" in the DNA code. These can be used to trace how DNA gets recombined, when it is passed from parents to offspring. SNPs can also provide clues needed to build a better genetic map of the human genome. See *Nature Genet* **14,** 367-370 (Dec 1996)x for the latest update on this technology (which appeared after this article had been submitted to the NewsLetter).

To date, about 150 SNPs have been identified that work "exceedingly well" as markers. Once 2,000 of these signposts are in hand, Lander says, a "***genomic scanner***" is planned, by putting all the SNPs on a single chip. It won't be too many decades before each newborn's genome can be scanned and everything--from predicting diseases and sensitivity to environmental agents to personality traits--will be known about that person!

Electromagnetic Fields (EMFs): You can't see 'em and they probably have no effect

Public concerns about possible health hazards from EMF exposures first arose in the late 'seventies, when researchers reported that children living close to high-voltage power lines in Colorado had increased rates of leukemia. Then there was an explosion of studies--most finding no health risks from ordinary levels of EMF exposure, but some finding everything from a slightly elevated risk of breast cancer and fallen arches to miscarriages. The National Institute of Environmental Health Sciences (NIEHS) just a few years ago sent out a Request for Applications (RFA) on EMF research.

At the request of the U.S. Congress, the Department of Energy (DOE) commissioned the National Research Council (NRC) to analyze the EMF data scientifically. Although EMFs at very high doses have been shown to disrupt chemical signaling between cells in culture and inhibit melatonin production and bone healing in animals, the ***NRC Panel found no adverse effects*** on cells or animals ***at the low EMF levels*** measured in houses (those either with a "high wire code" or located under power lines). A statement by the Bioelectromagnetics Society of 700 EMF researchers, however, was not surprising: "People may interpret the report [to mean that] the matter is settled, but we don't think it is." Two other groups--the U.S. Environmental Protection Agency (EPA) and the NIEHS--are scheduled to deliver further reports on the EMF subject to Congress in mid-1998.

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