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INTERFACE:
GENES AND THE ENVIRONMENT

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Racial and Ethnic Differences in Our Genes

"We must remember that what unifies us, far outweighs what makes us different. Skin color and body shape, language and culture, are all that differentiate the peoples scattered across the earth. This variety, which testifies to our ability to accept change, to adapt to new environments, and to evolve new lifestyles, is the best guarantee of a future for the human race. ...all this diversity, like the changing face of the sea or sky, is minute—when compared with the infinite legacy we human beings possess in common" — ***Francesco Cavalli-Sforza, 1995***

As the requisite 10-year U.S. Census took place at the start of the Year 2000, it seems appropriate that this Newsletter might look at how ***gene-environment interactions during human evolution*** have led to present-day "***categorization by racial and ethnic groups***." Instead of limiting respondents to the U.S. Census to a single race, the 2000 Census instructions allowed respondents to mark "one" or "more than one" from a list of 63 possible combinations of racial and ethnic groups. This new choice is expected to cause declines in population counts of "single-race groups" by: 3-6% for Whites, 3-7% for Blacks, 4-9% for Asians and Pacific Islanders, and 15-25% for American Indians. This seemingly small change in the Census form will have an enormous impact on population classifications in this country. For example, a large number of race-based public policies—including the redistricting provisions of the Voting Rights Act, equal employment opportunity laws, and affirmative action—may be affected by the estimated shift of some 8 million to 18 million U.S. citizens who will now claim "more than one race" instead of a single race.

This reclassification will impact not only population counts and the treatment of individuals, but also estimates of group characteristics (*e.g.* income, educational attainment, health status). For example, does someone who identified himself in 1990 as "White," and who now marks "White" and "American Indian," qualify for a minority small-business loan? Does someone who marked "Black" in 1990, but now marks "White" and "Black," no longer qualify for such a loan? Whereas the old system put the burden (of choosing a single race) on the individual, this new system will put the burden (of sorting out multiple races) on government, schools, and other institutions, as well as molecular epidemiologists and other users of racial data [*Proc Natl Acad Sci USA* **97:** 6230, 2000].

Definitions of 'Race' and 'Ethnic Group'

The term "race" originally came from Latin—gene***ratio*** (n) and gene***rare*** (v)—meaning "generation" and "to engender," respectively. Webster's Dictionary defines **race** as "any of the different varieties

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of mankind, mainly the Caucasoid, Mongoloid, and Negroid groups, distinguished by kind of hair and color of skin." Also, "any geographical, national, or tribal ethnic grouping." Some anthropologists regard Arabs, Jews, Latinos and Spaniards as "distinct races," whereas most would prefer to call these "ethnic groups." Most regard the origin of human races similar to that of animal or plant speciation, *i.e.* extreme geographic and genetic isolation for thousands of years without any outbreeding. Population geneticists have shown through blood markers that some Latino populations of Central and South America are "**trihybrid**," in that they have been derived from White, Black and American Indian—and only during the past 400 years (~20 generations).

In brief, therefore, "racial characteristics" is an ancient term, basically referring to "how one human being looks," or "is perceived," by another. This, combined with religious and geopolitical differences, has led to innumerable wars, slavery, suffering and misery throughout the ages. Although the subject of "race" can often be divisive, political, and emotionally explosive—perhaps some of these strong feelings can begin to be dispelled if one understands how these "races" have originated, especially how the development of each race has been influenced by the environment and evolution of human genes, and how much genetic admixture (mixing of genes) has actually been discovered between races in certain geographic areas.

Out of Africa — Twice?

Virtually all anthropologists now agree that the evolution of *Homo sapiens* began in Africa. The human lineage is estimated to have diverged from other primates about 5 million years ago, with the chimpanzee being our closest living relative. The most primitive human ancestors yet discovered belong to the genus *Australopithecus* (which includes "Lucy"), which lived more than 3 million years ago. Early members of our own genus, *Homo erectus*, and its near relative, *Homo ergaster*, arose about 2.5 million years ago in the same region of Africa (the Rift Valley) in which Lucy was discovered. These "archaic" hominids are thought to have migrated out of Africa approximately 1.7 million years ago to begin nucleus populations in Europe, the Middle East, and Asia [*Science* **288:** 948, 2000].

Fossils of *Homo sapiens*, dating between 200,000 and 80,000 years ago, have been found throughout the "Old World"—Africa, Europe, and Asia—and in New Guinea and Australia. These *Homo sapiens* shared with us important anatomical features (skull size and shape) and behavioral attributes (use of blades, bone tools, pigments and dyes, burial goods, art, trade, hunting, and distinct environmental resources). These humans subsequently scattered to Micronesia, Polynesia, and the "New World" (North and South America). Interestingly, the approximately 5,000 languages in existence today correspond closely to the differences seen between present-day nations and native tribes [Cavalli-Sforza, 2000].

The means by which modern humans (*Homo sapiens sapiens*) emerged is a matter of debate between proponents of two opposing theories. Supporters of the ***Multiregional Theory*** contend that modern human populations developed independently from archaic hominid populations (*Homo erectus* or *Homo ergaster)* in Africa, Europe, and Asia**;** early modern groups evolved in parallel with each other, and there was "gene flow" between these groups to give rise to present populations. On the other hand, supporters of the ***Displacement Theory***, commonly known as "Out of Africa" [*Nature Genet* **23:** 437, 1999], contend that contemporary human populations are derived from a single modern population group that left Africa between 200,000 and 80,000 years ago. This founding group migrated throughout the Old World, displacing any surviving archaic hominids. Recent studies on mitochondrial DNA, for example, have shown convincingly that Neanderthal man (*Homo neandertalensis*) existed in Europe as recently as 29,000 years ago but interbred very little, if any, with *Homo sapiens* [*Nature Genet* **26:** 144, 2000]. Hence, although almost all scientists agree that our early hominid relatives arose in Africa, most disagree on when the direct ancestors of present-day humans left Africa to populate the entire planet.

Our Perception of 'Race'

"Geography determines history" — ***Napoleon***

Eighty thousand years of *Homo sapiens* history translates to approximately 4,000 generations, which is easily sufficient for allelic differences in genes to evolve—genes that encode such characteristics as skin color, type of hair, or body size and shape. For example, the African pygmy is small with dark skin, highly coordinated and agile, elongated eyes and large nostrils, traits that in all likelihood were selected for optimal success while hunting-and-gathering in a very humid tropical climate (the surface area of a small body is greater in relation to its volume, enabling more efficient heat exchange). The Eskimo has more subcutaneous fat, skin lighter than that of the pygmy, narrow eyes and small nostrils, again to improve his likelihood

of survival in a very cold dry climate (heat is conserved through extra body fat; narrow eyes and small nostrils minimize heat loss while breathing). Lower levels of skin pigment may have evolved and been selected for in Northern European populations eating a vitamin D-poor cereal-based diet in locations where the sun exposure is low.

How many genes might determine skin color, hair color and texture, facial traits, and body size and shape? From genomics research, it now appears highly likely that surprisingly few genes might determine most characteristics that contribute to one's perceived racial stereotype. Between 40,000 and 140,000 genes are estimated to comprise the entire human genome, yet as few as dozens—several hundred at most—are likely to be found responsible for most racial features [*Science* **286:** 451, 1999]. Clearly, dark skin has evolved and been selected for in tropical populations, possibly as protection against tropical sun. The case for differences in skin color has now been linked to the melanocortin-stimulating hormone receptor-1 (*MC1R*) gene. Skin color is largely determined by the ratio and concentrations of different melanin pigments made in melanocytes (melanin-producing cells). The *MC1R* gene has multiple alleles, and certain alleles are seen in 80% of people with red hair—and skin that burns rather than tans**;** these same alleles are seen in less than 4% of Caucasians who tan rather than burn, and are never seen in Africans, suggesting that variant alleles in the *MC1R* gene are probably an adaptation to differences in sun-exposure levels in these distinct populations [*Am J Hum Genet* **66:** 176, 2000]. It is anticipated that differences in hair color and texture, facial structure, and body size and shape between human races might also be controlled by alleles of a small number of genes that affect these superficial, visible differences**;** the same is predicted to be true for alleles of genes that do not affect superficial racial or ethnic features (*e.g.* blood pressure, taste receptors). The true variations between human races are expected, therefore, to be only minor sequence deviations in receptor, transporter, metabolism, developmental signal transduction, transcription factor, or some equivalent, genes. Interestingly, this emerging concept is consistent with the hundreds of ethnic studies of drug-metabolizing enzymes [*Advanc Drug Res* **23:** 1, 1994] that generally show no more than 2- to 3-fold differences between races or ethnic groups—whereas differences between individuals, within any one race or ethnic group, are often 10- to greater than 40-fold.

Recent knowledge in DNA resequencing and human genetics have made us realize that the races that comprise *Homo sapiens sapiens* are far more amalgamated than had previously been imagined. An average population from any urban area in the world is expected to include about 85% of all human variant alleles. Differences among populations from the same continent contribute another 6% of the variability, and from different continents 9% to 13% of genetic variation [*Genetics* **131:** 479, 1992]. This means the popular perception that "human races are genetically distinct, that is, *unrelated* to each other" is largely false**;** this would be especially true in countries that are "melting pots" for numerous ethnic groups—such as the United States.

For many years now, the National Institutes of Health (NIH) has strongly urged the inclusion of minorities and ethnic groups in any clinical study. There are two major points to this article—first, that, instead of political reasons, there are scientific reasons to include racial and ethnic groups in certain kinds of clinical studies. Second, as we understand the large number of common alleles in individuals from different ethnic groups, there will be compelling reasons to study highly discordant individuals based on the quantitation of their trait (*e.g.* high metabolizers versus low metabolizers of a given drug or environmental chemical) rather than on their ethnicity.

The case for using ethnic populations

There are scientifically valid reasons for choosing to perform certain types of genetic studies in populations with relatively low allelic variation. Principal among these is that certain disorders are disproportionately more common in certain ethnic groups. Examples include cystic fibrosis in Northern Europeans, Sickle-cell disease in certain African sub-groups**,** and Tay Sachs disease in Ashkenazi Jewish populations. Using populations that have relatively high genetic admixture may require sifting through "genetic noise," which might be circumvented by the use of appropriate genetically "restricted" populations. Thus, NIH-mandated "ethnic inclusion criteria" might be the equivalent of a scientist required to study randombred or outbred mice, when a comparison of two inbred mouse strains would offer much less background noise—thereby more likely to reveal important genetic differences. For example, it was recently estimated that the European admixture in African-Americans living in the U.S. is, on average, about 26% [*Hum Genet* **104:** 149 (1999)], whereas individuals living in Sub-Saharan rural Africa show close to 100% African alleles [*Proc Natl Acad Sci USA* **96:** 1621

(1999)]. This means that some African-Americans residing, for example, in Chicago or Los Angeles might have 40% or 70% Caucasian alleles, while others might have 5% or 10%. Conversely, what percentage of African (or American Indian, or Asian) alleles might be present in the average U.S. "Caucasian" citizen?

The case for using populations classified by "phenotype" rather than ethnic origin

In many cases, variation of a trait between individuals within a "race" is much greater in magnitude than the mean variation between "races." This is particularly true of multifactorial traits, which may be influenced, and, to differing degrees by several genes, as well as environmental factors. In such instances, the restriction of the study population to a particular "race" or ethnicity would clearly limit the effectiveness of the study. In the future, it is predicted that specific human pharmacogenetic or ecogenetic phenotypes—*e.g.* CYP2D6 poor metabolizers (PMs) versus extensive metabolizers (EMs), or slow versus rapid N-acetylators—might represent more well-defined and genetically distinct populations than particular "racial" or "ethnic" populations. The biggest difficulty with the use of mixed populations is the possibility of disregarding epistatic (hidden genetic) effects (*i.e.* the "sensitive" allele in one genetic background need not be the "sensitive" allele in another background), and overcoming this drawback presents researchers with a major challenge.

The most important goal for the researcher in clinical studies of ethnic groups, therefore, is to recognize and understand each of the racial and ethnic groups that are chosen for study, in order to correctly interpret data. Some groups (*e.g.* African-American, Caribbean, Panamanian) might be expected to exhibit a large degree of allelic diversity, whereas other groups (*e.g.* sub-Saharan African, Inuit, Finn) would be expected to show much less richness of diverse alleles.

Summary

In conclusion, the concept now emerging at the end of the millennium is that the total number of genes encoding all the features related to "categorization of race or ethnic group" (skin color, hair color and texture, facial traits, and body size and shape) will probably be quite small (*e.g.* in the dozens, or several hundred at most)**;** the same is predicted to occur in genes that code for non-visible traits (*e.g.* blood pressure, taste receptors). Because of an unexpectedly large amount of genetic admixture (mixing of genes of one "race" with those of another "race") in most racial or ethnic groups, NIH must rethink its mandates that minorities and ethnic groups be included for political reasons as "distinct groups"—***in each and every clinical study***. To mandate this in every clinical study can increase the amount of "genetic noise" and lessen the likelihood of the researcher to gain a clear understanding of the clinical data. The idea of grouping by ethnicity certainly has its advantages, however, and may not be an unwarranted starting point in most population-based studies. It therefore becomes imperative for the clinical researcher to be aware and appreciate the richness of the diversity of alleles that exists (but to very differing degrees) in each and every racial and ethnic group, rather than to study such groups with the idea that they are genetically "pure." There may be advantages, in some cases, to search for allelic effects in relatively un-admixed populations**;** there might be advantages, in other cases, to search for allelic effects in more diverse (admixed) populations.

Ultimately, we will need to know the pertinent (medically relevant) genotype for all populations or individuals under medical care, in order to make the best decisions in care and prevention. This should be accomplished by mechanisms based on scientific reason and genetics, rather than NIH-mandated (for political reasons) "racial inclusion" in all human studies.

—Contributed by Daniel W. Nebert, MD and Anil Menon, PhD ... with special thanks to Tom Boat, Tom Doetschman, Lucia Jorge, Alvaro Puga, and Randy Sallee for their thoughtful reviews and helpful comments.

Suggested further reading:

Cavalli-Sforza LL, Cavalli-Sforza F, 1995, The great human diasporas: the history of diversity and evolution. Addison-Wesley Publishing Company, Inc., New York, 300 pp

Cavalli-Sforza LL, 2000, Genes, peoples, and languages. North Point Press (Farrar, Straus and Giroux), New York, 240 pp

...all life is worthy of respect..... the daily struggles, defeats, and successes of a survivor are greater than the victories of professional athletes and finally, it is the struggle itself that gives life dignity.....
.....from...Frederick Linge)

Genomically Speaking, ...

The crescendo in genome-sequencing this past year has made it almost impossible to stay on top of what is happening. This explosion in exciting news has been a major reason why we have chosen to have a "combined winter/spring issue" rather than just a "winter issue." Here are some of the whirlwind highlights, provided chronologically**:**

We have chosen to do the same with some of the other subjects in this issue, as well.

October 1999. **Celera Genomics** (Rockville MD) announces that it has sequenced some 1.2 billion base-pairs (**bp**) (about a third) of the human genome and that this information was being released to private subscribers.

November 1999. Celera announces it has completed the sequencing of the genome of the fruit fly *Drosophila melanogaster*. About 45 bioinformatics experts, protein specialists, and biologists convene in Rockville, Maryland, at a "***jamboree***" to help classify and name all the ~13,600 genes.

December 1999. The complete DNA sequence of the first human chromosome, #22 (the smallest), is reported by the federally-funded **Human Genome Project** (**HGP**)**:** twelve contiguous segments spanning 33.4 megabases (**Mb**) contain only 545 genes and an unexpectedly high number (134) of pseudogenes [*Nature* **402:** 467, 489, 1999].

The tiny mustard, *Arabidopsis thaliana*, will be among the first plant genomes to be sequenced. The whole genome is about 120 Mb, on five chromosome pairs, and is expected to encode ~25,000 proteins. The sequence of chromosomes 2 and 4, expected to have 31% of all the genes, are now reported [*Nature* **402:** 731,761, 769, 1999].

A list of 19 bacterial genomes, which have been sequenced or are in the final stages of completion, is listed in *Nature Biotechnol* **17:** 1168, 1999. The genome of the most radiation-resistant bacteria known, *Deinococcus radiodurans*, has been completely sequenced [*Science* **286:** 1571, 1999].

After the genome is sequenced, the field of ***proteomics*** (the study of protein function) is expected to become very popular [*Nature* **402:** 715, 1999].

January 2000. Celera announces they have completed 90% of the human genome sequence**;** some HGP researchers comment that "it's the equivalent of putting several copies of the *Encyclopaedia Britannica* into a shredding machine."

Of the 19,293 predicted proteins in the nematode (*Caenorhabditis elegans*), only 7% (1,277 genes) have so far been studied at either the genetic or biochemical level**;** expression microarray and RNA interference (**RNAi**) assays are being quickly developed to characterize the function of all the rest of these genes [*Science* **287:** 52, 2000]. A new term becomes popular in the medical literature**:** these experiments are called "***mining*** the wealth of genomics data."

February 2000. New techniques for looking at the function of proteins through "data mining" of completed genomes continue to be developed [*Science* **287:** 1221, 2000].

March 2000. Any "hope of collaboration between the rival teams [Celera headed by J. Craig Venter, versus the HGP headed by Francis Collins] has broken down." The HGP announces it has "just passed the 2-billion-bp mark, which is about 70% completion" [*Science* **287:** 2396, 2000].

Celera announces that, even before finalizing the human genome sequence, it is set to embark on an ambitious new effort in proteomics—further ruffling the feathers of federally-funded researchers [*Science* **287:** 2136, 2000].

President Clinton and Prime Minister Tony Blair make strong statements that the human genome sequence "must be freely available to all humankind" and that patents "should only be awarded to applications in which significant utility is demonstrated." Stocks in biotech companies plummet.

Government-funded researchers report that the sequence of 2.6 Mb of DNA from the tip of the *X* chromosome of *Drosophila* contains 273 genes, one gene about every 10 kb [*Science* **287:** 2220, 2000].

Genome data mining**:** The genome sequence of *Drosophila melanogaster* is reported and compared with other complex genomes [*Science* **287:** 2185, 2000]. The nonredundant protein sets of flies and worms are similar in size and only twice that of yeast. *Drosophila* proteins can be assigned to 8,065 distinct families, about 5,000 of which are shared with *C. elegans*. The fruit fly has orthologs to 177 of the 289

human genes known to be mutated or altered in human diseases [*Science* **287:** 2204, 2000].

Wormbase, found at *http://www.wormbase.org*, is advertised as an example of a "vertical" database that integrates many types of information about a single organism. This site mirrors Flybase, set up several years ago for *Drosophila*.

April 2000. Celera announces it has "***completed*** the sequencing phase of one person's genome." Celera's stock, which had fallen abruptly in mid-March (after remarks by Clinton and Blair), once again soars. Critics maintain that "3.5-fold coverage of sequence is not the same as the 10X coverage that Celera promised in 1998," meaning that a lot of sequencing errors are expected to be found.

The recently published sequence of the *Drosophila* genome was reported to be contaminated with some human gene sequences! A Celera spokesperson says "it's no big deal" (it turned out to be about 150,000 bp—out of approximately 180 million bp sequenced).

The Department of Energy (DOE) announces that it has completed "working drafts of human chromosomes 5, 16 and 19."

The high degree of alternative splicing, which is being found in the human genome, makes it likely that there are going to be many more gene products (proteins) than genes. If humans have 100,000 genes, they might have 300,000 proteins [*Nature Genet* **24:** 340, 2000]!

Monsanto (in collaboration with the company of Leroy Hood in Seattle) surprises everyone by announcing it will release the rice genome sequence by mid-July to the International Rice Genome Sequencing Project (composed of researchers in Japan, China, India, Taiwan, Korea, Thailand, Canada, France, the United Kingdom and the United States).

May 2000. Functional conservation, among genes from the three model systems so far available—baker's yeast (*Saccharomyces cerevisiae*), nematode (*Caenorhabditis elegans*), and fruit fly (*Drosophila melanogaster*)—is so strong that the goal of the ***Gene Ontology Consortium*** (GO) is to produce a dynamic controlled vocabulary that can be applied to all eukaryotes, even as knowledge of gene and protein roles is accumulating and still changing [*Nature Genet* **25:** 25, 2000]. Likewise, shotgun sample sequence comparisons between mouse and human genomes are already showing that, once the human genome is complete, the mouse genome will follow very closely behind—because of DNA similarities across large stretches of DNA [*Nature Genet* **25:** 31, 2000].

The DNA sequence of human chromosome 21 is reported, again the low number of genes (only 225) plus 59 pseudogenes is a surprise [*Nature* **405:** 283, 311, 2000]. This has led to a "lottery," originating from a Genome Sequencing & Biology meeting at Cold Spring Harbor, as to who can guess the exact number of human genes**;** early entries ranged from less than 30,000 to more than 150,000 [*Science* **288:** 1146, 2000; *Nature Genet* **25:** 129, 232, 235, 239 (2000); *Nature* **405:** 264, 2000].

The On-line Mendelian Inheritance in Man (OMIM) reaches 1,000 gene entries containing at least one allelic variant identified as the cause of, or associated with, a recognizable human phenotype [*Nature Genet* **25:** 11, 2000].

Lateral gene transfers (genes from one species captured by another) are surprisingly common among bacteria and represent a significant means by which substantial amounts of DNA can be introduced into, or deleted from, bacterial chromosomes [*Nature* **405:** 299, 2000].

June. Portrayed these past 2 years as "the scientific rivalry of the century," the principal players of Celera and the HGP join together in a political move to bury their differences and make a joint announcement that "***a draft of the human genome has been completed***." The race to obtain a draft sequence of the entire human genome has been declared "an honorable draw" (the White House ceremony on June 26th was designed to heal a split in the research community between business and government). Following this choreographed joint announcement, they pledge to publish two draft sequences (simultaneously, but separately, before year's end), hold a joint meeting of the two research teams after these publications, and then promise to keep open all lines of communication forever after. The public consortium will finish the draft this year, but then produce a polished (99.99%) version by 2003 or sooner, while moving on as well to other organisms including the mouse and rat.

The 130-Mb *Arabidopsis thaliana* (plant) genome, with approximately 25,000 genes, is expected to be fully sequenced in July and published by year's end [*Science* **288:** 1715, 2000].

Cloning Animals, continued ...

December 1999. Teruhiko Wakayama, who had been in the laboratory of Ryuzo Yanagimachi at the University of Hawaii when they cloned the first mouse, has now cloned mice ***from embryonic stem (ES) cells*** at The Rockefeller University in New York [*Proc Natl Acad Sci USA* **96:** 14984, 1999]. It thus appears possible to clone from a single cell a large number of individuals over an extended period of time..!!

A frozen embryo of an endangered species, the African wildcat (*Felis sylvestris libyca*), has been transplanted into the uterus of an ordinary house cat and was successfully born [*Science* **286:** 2447, 1999]. The number of this species left in the wild is estimated to be "no more than 1000," thus raising hopes that this embryo transfer technique might help stave off extinction for some endangered species that reproduce poorly on their own but whose sperm and embryos can be stockpiled in the freezer as a last-ditch approach to saving the species.

January 2000. A U.S. company (Geron Corporation, California) received two British patents that appear to grant it commercial rights to create human embryos by cloning. Issued last week on the cloning method that produced Dolly the sheep, these precedent-setting patents have sparked protests from groups concerned about the ethics of biotechnology patents, especially those covering human genes or cells [*Science* **287:** 559, 2000].

A transgenic zebrafish line, carrying a shuttle vector plasmid for detecting mutagens in aquatic environments, does so by increasing the frequency of mutations in the target gene (the *rpsL* gene of the bacterium *Escherichia coli*) [*Nature Biotechnol* **18:** 62, 2000].

February 2000. Monkeys almost never have twins, and it would be advantageous to study clinical drugs in identical nonhuman primates. A new technique involves splitting rhesus monkey embryos at the 8-cell stage and separating them into four 2-cell embryos which are then implanted in surrogate mothers [*Science* **287:** 317, 2000]. However, although a 31% success rate in pregnancies was achieved, only one in four pregnancies resulted in live births so far.

Six calves were cloned from adult fibroblast cells that had been in culture for a long time [*Proc Natl Acad Sci USA* **97:** 990, 2000]. This study shows that fibroblasts of aged animals remain competent for cloning, and that prolonged culture does not affect the cloning competence of adult somatic donor cells.

April 2000. As discussed in previous issues of ***Interface***, it appears that when Dolly the sheep (who had been cloned from a 6-year-old ewe) was officially 3 years post-partum, all the cells in her body were in fact 9 years old. In contrast to cloned sheep, however, cloned cattle do ***not*** seem to be the age of the donor nucleus [*Science* **288:** 586, 2000]. The reason for this apparent difference between sheep and cows is not understood [*Nature Biotechnol* **18:** 594, 2000; *Science* **288:** 1775, 2000].

Pigs were cloned from adult cells, for the first time [*Nature Biotechnol* **18:** 365, 2000]. It is hoped that clinical trials for xenotransplantation of pig organs (into humans) can begin as early as 4 years from now.

May 2000. Cumulina, the first mouse to be cloned from an adult cell, died at the University of Hawaii, at age 31 months (the average mouse lives for only about 2 years), refuting the debate over whether there are effects of cloning on the aging process.

June 2000. A new technique, using the internal ribosome-entry site (IRES) that allows the mRNA produced from a transgene to be translated very efficiently into protein, looks promising in that transgenic sheep, for example, can be used as "mobile protein factories" by providing any medically important protein to be expressed at high levels in milk, meat, or wool [*Nature* **405:** 1004, 1066, 2000].

Environmental Endocrine Disruptors, continued.....

This subject has been covered, numerous times, in previous issues of our ***Interface*** Newsletter (as far back as issue #3, autumn, 1994), and the controversy rages on. Environmental estrogens are a particularly prevalent and potentially harmful source of endocrine disruptors that have been linked to feminization of wildlife such as fish and reptiles, and lowered sperm counts and the increasing incidence of breast and testicular cancer in humans, say Hock and Seifert [*Nature Biotechnol* **17:** 1162, 1999]. However, Safe contradicts this [*Environ Health Perspect* **108:** 487, 2000] by stating**:** analyses of North American data show that sperm counts have not decreased over the last 60 years, and no cause-and-effect relationship can be shown for environmental endocrine disruptors and hypospadias (penis defect), cryptorchidism (undescended testis), or cancer of the breast or testis.

Observations by a Biologist

1, 2, 3, ... Who's Counting?

Fingers. From evolutionary biology, several years ago it became clear that dinosaurs originated from birds. Among the most important features believed to link theropod dinosaurs and birds is the tridactyl hand—a hand reduced to three fingers. Yet, examination of fossils and skeletons confirms that the raking hand of theropod dinosaurs comprises ***digits 1-2-3*** (*i.e.* thumb and next two fingers, with digits 4-5 only in vestigial form) and the bird hand is composed of ***digits 2-3-4*** (with digits 1 & 5 in vestigial form). A frame-shift hypothesis has now been put forth [*Proc Natl Acad Sci USA* **96:** 5111, 1999], which seems to make a lot of sense**:** the developmental properties responsible for digits (D)1-D3 are shifted onto embryonic precartilagenous condensations (C)2-C4 in birds. Subsequently in the evolving dinosaur, C2 became D1, C3 became D2, and C4 became D3. By this proposed shift, birds can still be nested in the same clade as maniraptoran theropod dinosaurs.

The neck. In the human, mouse, bat and giraffe, the number of cervical vertebrae is the same**:** seven. Yet, the number of neck vertebrae in birds can vary strikingly, apparently depending on the needs of that species**;** for example, the swift has 13, and the swan has about 25, neck vertebrae. Why have mammals maintained a ***7-vertebra neck*** over millions of years of evolution? Frietson Galis (Leiden University, Netherlands) postulated at the Evolution '99 Meeting (Madison WI) that any alterations in the genetic program responsible for generating the seven cervical bones are the cause of a large increased risk in embryonic cancers**(!)** First, she listed epidemiological studies that have shown an association between neuroblastoma (a type of childhood tumor that arises from embryonic neural tissue) and congenital rib anomalies, and between childhood cancers and skeletal abnormalities in general.

Abnormal ribs are known in mice to be caused by disruption in one or another of the homeobox (*Hox*) genes. Increased rates of leukemia, and related cancers, have been found when the *Hox* gene regulator M11 is inhibited or when the *Hoxb8* gene is overexpressed. Increases in intestinal cancer were found when another *Hox* regulator, Cdx2, is missing. Taken together, these data suggest that *Hox* genes play a role in both skeletal organization and in tissue- or cell-type proliferation (leading to malignancies). If changes in *Hox* expression and number of neck vertebrae lead to childhood cancer, there would be an important selective advantage for mammals to stay with seven neck vertebrae. But, what about such mammals as sloths and manatees (having 6 to 9 cervical vertebrae), reptiles, and birds? Perhaps the wide variations from the 7-vertebrae neck found in almost all mammals might explain the "very low rates of embryonic cancer" in the sloth, manatee, reptiles and birds, Dr. Galis speculated.

We WELCOME these UC researchers to the CEG

Erik S. Knudsen, PhD, *Assistant Professor, Department of Anatomy, Neurobiology and Cell Biology.*

He is interested in the mechanism through which the retinoblastoma tumor suppressor, RB, inhibits cancer development. RB is a negative regulator of cell cycle progression which is functionally inactivated in the majority of cancers. Importantly, RB is also a critical environmental sensor responding to a plethora of signals. Understanding the action of RB and its regulation by the enviroment is critical in evaluating cancer development and therapy.

Mary Beth Genter, PhD, *Associate Professor, Department of Environmental Health.*

She is investigating drug metabolism, especially by the P450 enzymes in the olfactory epithelium of the mouse and rat, and various transgenic and knockout strains of mice. Currently she is investigating mechanisms of olfactory mucosal carcinogenesis of a widely-used class of herbicides.

Ying Xia, PhD, *Assistant Professor, Department of Environmental Health.*

Her laboratory will study the intracellular signaling pathways concerning cell responses to physiological, pathological and environmental stimuli. In particular, she will focus on the regulation and function of mitogen-activated protein kinases (MAPKs). MAPKs have been related to important biological functions, such as proliferation, differentiation and apoptosis, via their abilities to phosphorylate transcription factors, therefore modulating gene expression. One group of MAPK, c-Jun N-terminal kinases (JNKs), is of particular interest because their activities are strongly enhanced by growth signals as well as environmental stresses, including ultraviolet light, hyperosmolarity, and oxidative stress. She will study the regulation and the biological implications of the JNK pathway.

Daniel Prows, PhD, *Assistant Professor, Department of Environmental Health*

Dr. Prows is interested in determining the genetic factors controlling susceptibility to acute lung injury, a condition that frequently results in death. Using a mouse model and exposure to ozone, several chromosomal regions have been identified which contain loci linked to survival of acute lung injury. He will narrow these genetic intervals to a level amenable to physical mapping by generating congenic lines of mice and examine genes in the identified regions of interest for their possible role(s) in susceptibility to acute lung injury.

Recent Highlights

The following includes various studies and recent reports—relevant to the theme of genes and the environment—which caught our eye and we believe are worthy of note**:**

- A satellite DNA-based artificial chromosome (SAT-DAC) has been developed that allows researchers to insert virtually any gene into mammalian cells without the risk of disrupting other genes at the site of integration [*Nature Biotechnol* **17:** 1149, 1999].
- A new reporter gene (*cobA* from the bacterium *Propionibacterium freudenreichii*)—has been tested in bacteria, yeast or mammalian cells—and shown to result in bright red fluorescence that can be visualized with standard fluorescence microscopy and fluorescence-activated cell sorting analysis at the single-cell level [*Nature Biotechnol* **17:** 1175, 1999].
- IBM announces a $100-million project to build (in less than 5 years' time) a computer, which would be about 500 times faster than today's most powerful computer [*Nature* **402:** 705, 1999].
- The high death rates seen in cloned animals could be due to ***heteroplasmy***, *i.e.* the condition of mismatched mitochondria [*Nature* **402:** 371, 1999].
- The origins and relationships of flowering plants and their phylogeny have been explored**;** flowering plants appear to have originated approximately 90 million years ago—about the same time as "the great mammalian radiation" [*Nature* **402:** 358, 1999].
- The latest research shows that *BRCA1* and *BRCA2* (which function as breast tumor suppressor genes) are also required for embryonic proliferation [*Trends Genet* **16:** 69, 2000].
- Looking at cells from healthy people of various ages and from children with progeria (an accelerated form of aging), researchers used ***microarray analysis*** to show that just 61 genes—out of a total of some 6,300 genes examined—change with age [*Science* **287:** 2390, 2000]!
- Scientists have developed Parkinson Disease models in the mouse and fruit fly, comparing the phenotypes in these two model organisms with that in the human [*Science* **288:** 631, 2000].
- Some 30 laboratories (with little previous DNA sequencing experience) in São Paulo, Brazil, shocked the world by reporting in April they had sequenced 2.7 million base-pairs (~2800 genes) of *Xylella fastidiosa*—the first genome of a bacterial plant pathogen ever to be sequenced. This bacterium causes a disease, citrus variegated chlorosis, which threatens the entire industry in São Paulo, the world's largest exporter of orange juice concentrate [*Science* **288:** 801, 2000].
- Evidence continues to mount that antibiotic use in agriculture (giving antibiotics to pigs, cows, etc) is leading to the emergence of more "superbugs"—bacteria acquiring resistance to drugs that are causing increasing numbers of deaths in humans [*Science* **288:** 792, 2000].
- A new method has been developed for converting a diploid chromosome set to a haploid state, allowing highly reliable testing for mutations [*Nature* **403:** 723, 2000].
- Mice lacking the vanilloid receptor-1 (*Vr1*) gene exhibit an amazing tolerance for hot sauce**;** for example, they drank capsaicin-laced water freely but still showed extreme sensitivity in response to pain caused by inflammation [*Science* **288:** 241, 306, 2000].
- The three-dimensional representation of the structural elements of a basic-helix-loop-helix (**bHLH**) protein has been surmised. More than 250 of these bHLH transcription factors—including the ***Ah receptor***—have been discovered throughout the animal kingdom so far [*Nature* **404:** 715, 2000].
- The family of "bitter taste receptors" has been cloned and characterized [*Nature* **404:** 601, 2000; *Cell* **100:** 693, 2000; *Cell* **100:** 703, 2000]. A defect in one of these receptors is likely to explain the ***phenylthiourea (PTU) "nontaster"*** autosomal recessive trait—which was described in 1932 as perhaps the first pharmacogenetic difference in humans.
- A new plastic, from the carbon stored in plant sugars, is environmentally competitive with conventional hydrocarbon-based polymers in terms of cost and performance. Polylactide (PLA) will be mass-produced by Cargill and Dow Chemical by late 2001. Corn is the current source of the polymer feedstock, but rice, wheat, sugar beets, and even agricultural waste can be used to produce PLA. The production of PLA requires 30% to 40% less fossil fuel than tradi-

tional plastics production and decreases net CO_2 emissions dramatically [*Environ Health Perspect* **108:** A209, 2000]!

- More sophisticated and specialized search engines are promised, in the near future, to help scientists surf the web [*Nature* **405:** 112, 2000].
- Genetically modified plants were shown to become completely resistant to nematode infection (the worms need cell division in order to invade successfully) by tricking the invading worms to turn on a cell cycle inhibitor [*Science* **288:** 2309, 2000].
- The human telomerase (h*TERT*) gene is being increasingly used to immortalize cells in culture, but it does so by activating the oncogene c-*MYC* and inactivating the tumor suppressor gene *TP21* [*Nature* **405:** 755, 2000]. Thus, the use of h*TERT* for expansion of normal human cells for therapeutic purposes must be approached with caution!
- A study of "virtual twins" (pairs of unrelated siblings who have been raised together but have few common genes) shows that intelligence (IQ) is strongly influenced by genetics and very little by the environment. Correlation coefficients were 0.26 for virtual twins, 0.50 for related siblings, and 0.86 for identical twins [*Science* **288:** 1735, 2000].
- Transgenic plants harboring the *CYP2E1* gene (which metabolizes halogenated hydrocarbons) were shown to increase the breakdown of trichloroethylene (TCE, one of the most widespread groundwater contaminants in the U.S.) by as much as 240-fold [*Proc Natl Acad Sci USA* **97:** 6287, 2000]..!!
- Our first issue of ***Interface*** (winter 1993-94) proposed that allelic differences in the human paraoxonase (*PON1*) gene might explain differences in the response of soldiers exposed to the nerve gas sarin during the Gulf War, causing the "Gulf War Syndrome." Experimental evidence continues to accumulate and support this association [*Toxicol Appl Pharmacol* **157:** 227, 1999; *Genome Res* **10:** 153, 2000].

"Quote of the Month ....."it has often been said there's so much to be read, you never can cram all those thoughts in your head, so the writer who breeds more words than he needs, is making a chore for the reader who reads, so that's why my belief is the briefer the brief is, the greater the sigh of the reader's relief is"..... *Dr. Seuss, 1904-1991*

Human Diversity, continued ...

March 2000. The latest estimate is that a single-nucleotide polymorphism (SNP) is expected to occur, on average, every 1000 base-pairs (bp) throughout the 3 billion bp in the human genome (but SNPs can occur one in every 25 bp for one gene and one in 2000 bp for another gene. This means about 3 million SNPs are now anticipated. One SNP every 30 kb appears to be sufficient to pinpoint genes involved in complex diseases such as psoriasis, migraine, Alzheimer disease, and diabetes [*Science* **287:** 1898, 2000]. A database, containing 600,000 SNPs so far, is freely available on the web at http://hgbase.interactiva.de/about.html

An analysis of wrist bones of early human fossils [*Nature* **404:** 339, 2000] has now provided the first good evidence that humans evolved from ancestors who "walked on their knuckles," as the chimpanzee and gorilla do today.

April 2000. As described in previous NewsLetter issues, the Human Genome Diversity Project (**HGDP**) is a bold scheme to collect, store and analyze DNA representing the world's ethnic diversity. This project now seems unlikely to happen, without more funding and broader political support [*Nature* **404:** 912, 2000]. Luigi Luca Cavalli-Sforza is Chair of HGDP, but others have criticized the program as "not having clearly defined goals and questions." Cavalli-Sforza says that the work he and Walter Bodmer (University of Oxford, and supporter of HGDP) have done shows that diversity research is healthy (as is also discussed in the Feature Article of this issue of ***Interface***).

June 2000. One theory about the evolution of languages across the Pacific Ocean during the past 6,000 years is called the "express-train"—in which a language was inherited from a common ancestor and then spread eastward from southeast Asia and China outward toward Polynesia and the Marshall Islands. Using parsimony analysis of a matrix of 77 Austronesian languages with 5,185 lexical items [*Nature* **405:** 1008, 1052 , 2000], Gray and Jordan produced a topology tree that is highly compatible with this express-train model.

When, and where, were cereals first domesticated? DNA studies of the remains of wild forms and their domesticated derivatives [*Science* **288:** 1602, 2000] strongly suggest that einkorn and emmer wheat, barley, chickpea, lentil, bitter vetch, flax, and possibly pea all originated between 11,000 and 10,000 years before the present (B.P.) in the Jordan Valley and adjacent areas of the southern Levant (in present-day Israel and Jordan). Perhaps it was the changing climate (to cooler and drier weather at this time) that helped trigger the end of a nomadic lifestyle and the beginning of farming settlements.

CEG Members in the News

Ranjan Deka was elected to the Editorial Board of Human Biology and selected to serve on the NSF Advisory Panel for Physical Anthropology for the period April 1, 2000 - March 31, 2002.

Tom Doetschman became Chairman of the subcommittee to establish a Repository for Mouse Models of Human Cancer. The committee was established by the National Cancer Institute's Mouse Models of Human Cancer Consortium. He also became a consultant for the establishment of a Stem Cell Research Institute at the University of Nebraska Medical Center in Omaha.

Mary Beth Genter was appointed to the Society of Toxicology Placement Committee (3-year appointment) beginning in April, 2000.

Sohaib Khan gave a seminar entitled: "Mechanism of estrogen receptor action: role of the F-domain" at the Karolinska Institute (Stockholm, Sweden) in April, 2000.

George Leikauf gave the following invited lectures: "Microarray analysis of positional candidate genes" NIEHS DERT Retreat, Pine Needles, NC, January, 2000; "Genetics of acute lung injury" Department of Environmental Health, University of Washington, Seattle, WA, January, 2000; "Gene-environmental interactions in lung injury" New York University, Tuxedo, NY, February, 2000; "Genomic analysis in pulmonary pathology" University of Cincinnati, Department of Pathology and Laboratory Medicine, Cincinnati, OH, February, 2000; "Functional genomics of acute lung injury" Pulmonary Biology Program, Children's Hospital Medical Center, Cincinnati, OH, March, 2000; "Grand Rounds: Functional genomics of acute lung injury" New York University: Bellevue Hospital, New York, NY, March, 2000; "Genome wide analyses and cDNA microarray in pulmonary pathobiology" at the Emerging Technologies in Molecular Biology and Their Application for Environmental Health Issues Mini-symposium during the Health Effects Institute Annual Conference, Atlanta GA, April, 2000; "Functional genomics of acute lung injury" at the University of Cincinnati, Department of Environmental Health, Cincinnati, OH, April, 2000.

Frank McCormack was elected to the American Society for Clinical Investigation, an honor society for physician investigators. The induction took place in early May.

Anil Menon served on the Experimental Cardiovascular Study Section and on the American Heart Association (National) Study Section. He also presented invited talks at the Biology of Aquaporins/MIP 2000 meeting, (Göteborg, Sweden), and received funding of new RO1s: "Role of sodium channels in African-American hypertension" and "Role of aquaporin-5 in fluid balance."

Dan Nebert was an invited speaker in the session on "Human Susceptibility and Mechanistic Toxicology" at the Environmental Protection Agency/Department of Defense (EPA/DOD) Annual Conference on Toxicology (April, 2000, Cincinnati, Ohio), an invited speaker at the International Federation of Clinical Chemistry (IFCC)-Roche Joint Conference "Human Genomics, the Basis of the Medicine of Tomorrow: Validating and Using Pharmacogenomics," (April, 2000, Kyoto, Japan), and an invited speaker in the session on "Emerging Biomarker Methodologies," International Conference on Arctic Development, Pollution and Biomarkers of Human Health, sponsored by the National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, and the Arctic Monitoring and Assessment Program (May, 2000, Anchorage, Alaska).

Alvaro Puga chaired a session and gave a talk entitled "Ah receptor signaling in cell cycle progression" at the 3rd International Symposium on Signal Transduction Pathways held in Luxembourg, January, 2000. He was elected a Councilor of the Molecular Biology Specialty Section of the Society of Toxicology. He was also a member of the Program Committee for the Society of Toxicology annual meeting and a member of the Editorial Board of Cardiovascular Toxicology. He delivered a lecture on "The transcriptional signature of dioxin in human hepatoma HepG2 Cells" at the Society of Toxicology annual meeting in Philadelphia, March, 2000.

Howard Shertzer was a grant reviewer for the Army Breast Cancer Initiative for 2000 as an Epidemiology Panel Member.

Peter Stambrook chaired the "Transgenics" session at the Environmental Mutagenesis Society meeting in April, 2000 (New Orleans, Louisiana).

James Stringer was an invited speaker at the Transgenesis session during the 31st Annual Meeting of the Environmental Mutagenesis Society April, 2000 (New Orleans, Louisiana).

Nancy Steinberg-Warren received the Excellence in Teaching Award, College of Allied Health Sciences, UC, 1999-2000, as well as funds from the March of Dimes and the Ohio Dept of Health to conduct a community-based folic acid education project with the mission to reduce the incidence of neural tube defects.

Susan Vandale and **Eula Bingham** have had COEP articles accepted for publication, and the LEGENDS project web site was chosen as a new profile added to the "EFS Profiles." This database outlines 200 sustainability initiatives of higher education institutions, documenting efforts and accomplishments in community involvement, curriculum change, greening the campus, institutional transformation, and sustainability research.

David Warshawsky has accepted an invitation to be the local organizer for the 18th International Symposium on Polycyclic Aromatic Compounds September 9-13, 2001, which will be hosted by the University of Cincinnati.

Legally Speaking, ...

January 2000. What sort of genetic information is able to be patented? The U.S. Patent and Trademark Office (PTO) proposed a policy that will raise the bar for such patent applications [*Nature* **403:** 3, 2000; *Science* **287:** 1196, 2000]. NIH officials and many other publicly funded scientists argue that "no DNA patent should be granted unless researchers know the gene's full sequence and have figured out what protein it produces and what that protein does in the cell." Of course, the *BRCA1* and *BRCA2* genes were discovered more than 5 years ago, are known to increase one's genetically inherited risk in a small percentage (~5%) of breast cancer, yet studies still have not determined completely all the functions of these transcription factor proteins in various cell types!

February 2000. Some believe that disease-causing mutations are easier to find in genetically homogeneous populations, such as that of Iceland, whose genomes have less "noise" than those of more diverse societies. In December 1998, Iceland's parliament approved the creation of the database and, recently, gave one company, ***deCODE***, exclusive rights to run it. Now, a small biotech start-up is providing an alternative to those critics who want to mine Iceland's genetic riches but dislike the arrangement with deCODE. The company is called ***UVS***—after the three witches Urdur, Verdandi and Skuld who, according to Icelandic legends, determine the fate of man [*Science* **287:** 951, 2000].

A computer model calculated that genetically modified (**GM**) fish—bigger but less viable—could pass on inferior traits to a wild population. The simulation showed that 60 transgenic fish having the growth hormone (*GH*) gene could thus lead to the extinction of a population of 60,000 fish in 40 generations [*Nature Biotechnol* **18:** 143, 2000].

March 2000. The *New York Times* provided results from a recent poll indicating that, whereas 83% of Americans generally support the teaching of evolution in public schools, 79% think that creationism also has a place in the public-school curriculum [*Nature Genet* **24:** 337, 2000]..!!

April 2000. Amgen (Thousand Oaks, CA) developed the drug Epogen(R) by cloning the human erythropoietin (*EPO*) gene, inserting it into Chinese hamster ovary cells, and producing the hormone (which stimulates production of red blood cells). Transkaryotic Therapies (TKT, Cambridge MA) have inserted a promoter (or, "on" switch) into human cells that can turn on the *EPO* gene and produce the hormone. Amgen is now suing TKT for infringement of several patents on its Epogen, but TKT claims that its production process is distinct from that of Amgen, so it is not infringing on that company's patents (in fact, TKT's process does not even require knowledge of the *EPO* gene sequence) [*Nature* **404:** 532, 2000].

The U.S. National Research Council (NRC), the research arm of the National Academy of Sciences, released a study on the safety of GM food. The study endorses the main conclusions of a 1987 NRC paper on the subject, that "an organism's properties, rather than the process by which it was produced, are the key to its safety." Far more research into the environmental impacts of GM foods is also called for. The NRC also announced a new standing committee to maintain surveillance of agricultural biotechnology issues [*Nature* **404:** 693, 2000]. Not unexpectedly, critics in some environmental groups claim the NRC panel was biased.

The biggest ever zebrafish-screening program has begun at the Max Planck Institute for Developmental Biology (Tübingen, Germany). The researchers plan to expose the fish to mutagenic chemicals, then breed them and scan 17 million fish over the next year. These studies are expected to uncover genes that are critical during development [*Science* **288:** 607, 2000].

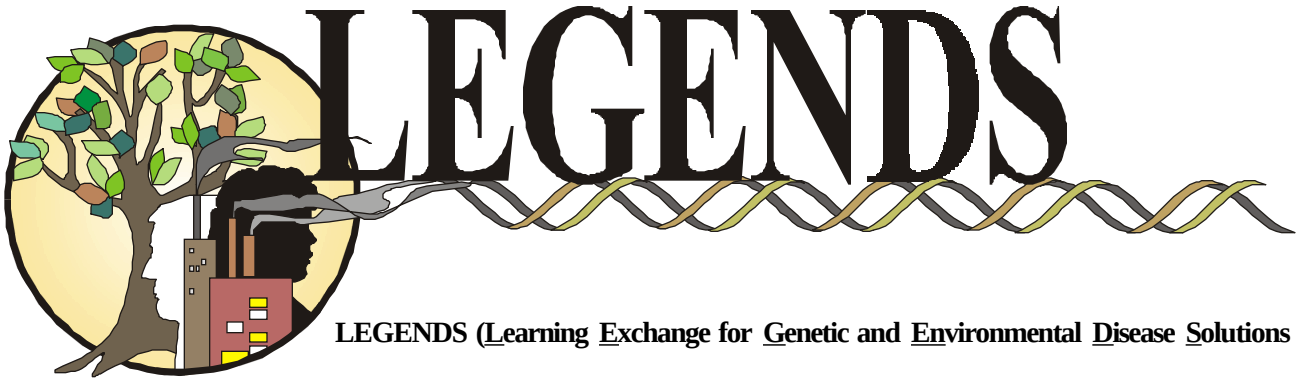
May 2000. Human Genome Sciences, Inc. (Rockville, MD) was issued a patent on the CCR5 chemokine receptor—simply because there was homology with other chemokine receptors. Later, it was found that CCR5 is ***the*** key receptor for HIV, and the U.S. Patent and Trademark Office (PTO) is now being asked to overturn this patent because it "could stifle further innovation in this field" [*Nature* **405:** 3, 2000]. It remains to be seen how far the PTO can go in dealing with such cases.

A poll (run by the professional polling organization NOP) showed that 46% of people "would personally eat food if they knew it was genetically modified or contained GM ingredients," as compared with 50% who said they would not. Polls run by environmental groups, in contrast, show that 75% to 85% of the people they spoke with are against GM foods [*Nature Biotechnol* **18:** 475, 2000].

June 2000. More on the deCODE contro-

versy**:** "Individual persons have the ethical and legal rights not to be research subjects without their voluntary, competent, informed and understanding consent. Research should not be conducted on a population, even research related to migration patterns or the evolution of a genome, unless the benefit to the population is likely to outweigh the risks" [*N Eng J Med* **342:** 1830, 2000]. Although 10% were originally against the government giving the country's genetic database to a single company, only 7% of the Iceland nation has since opted out of the database [*N Eng J Med* **342:** 1827, 2000]. The Icelandic experience thus shows that people are indeed concerned about how genetic research is done, that "medical-records research" and "DNA-based research" are not the same, and that community consultation is necessary but not sufficient to justify DNA-based research ethically. The Icelandic experience also demonstrates that the probable benefits of such research should be spelled out as clearly as possible and that international standards for consent to, and withdrawal from, such research should apply directly to research on human genetic variation. Moreover, these rules should continue to remain relevant, even after it becomes possible to transfer all the genetic-sequence information in a DNA molecule to a computer disk.

What sort of genetic information is able to be patented? Those who oppose patents on genes give four reasons for their position**:** [a] genes exist in nature, as our natural heritage, and therefore should not be "owned" by any individual or group**;** [b] genes are discoveries rather than inventions**;** [c] because they exist in nature, genes cannot be considered "new"**;** [d] gene isolation and cloning is such a well-established technique that it is no longer "inventive" to do it. The debate on gene patenting, while still unresolved, is simplified in this nice article [*Nature Biotechnol* **18:** 683, 2000].



LEGENDS (Learning Exchange for Genetic and Environmental Disease Solutions

Susan E. Vandale, Eula Bingham. A Curriculum for Environmental Genetics Education. [*Am J Prev Med* 19: 197, 2000]

Environmental genetics is a scientific area concerned with interactions between genes and the environment. Progress in this field, coupled with the growth in genetic testing, have great potential for improving human health. There are also ethical, legal and social concerns surrounding advances in environmental genetics and genetic testing. Since genetic information is rapidly expanding in our society, the public needs to learn more about scientific progress and policy issues in these areas.

The article describes a curriculum for the public on environmental genetics and genetic testing. In 1998, the Department of Environmental Health (Center for Environmental Genetics), University of Cincinnati, began an outreach project for the public called **LEGENDS** (**L**earning **E**xchange for **G**enetic and **En**vironmental **D**isease **S**olutions). The project fosters awareness and understanding on environmental genetics and genetic testing with discussion of related policy issues. The curriculum includes brief lecture-discussions around thematic modules and a set of interactive exercises to be conducted in small groups. At the time of this publication, more than 175 persons have participated in **LEGENDS** workshops. The article published in the mentioned journal describes the project and suggests that the curriculum is a potentially useful resource for educating the public about environmental genetics, genetic testing and related policy issues.

SCIENCE LITE...

REMEMBER THE GOOD OL' DAYS..??

A ***computer*** was something on TV,
From a science fiction show of note.
A ***window*** was something you hated to clean,
And ***ram*** was the cousin of a goat.

Meg was the name of my girlfriend,
And ***gig*** was a job for the nights.
Now they all mean different things,
And that really ***mega bytes***.

An ***application*** was for employment.
A ***program*** was a TV show.
A ***cursor*** was someone who did profanity.
A ***keyboard*** belonged to a piano.

Memory was something you lost with age.
A ***CD*** was a bank account.
And if you had a ***3-inch floppy***,
You hoped nobody would find out.

Compress was something you did to garbage,
Not something you did to a ***file***.
And if you ***unzipped*** anything in public,
You'd be in jail for a while.

Log on meant adding wood to a fire;
Hard drive was a long trip on the road.
A ***mouse pad*** was where a mouse lived,
And a ***back-up*** happened to your commode.

Cut you did with a pocket knife,
Paste you did with glue.
A ***web*** was only a spider's home,
And a ***virus*** gave you the flu.

I guess I'll just stick with pad and paper,
And the ***memory*** of my head.
I hear nobody's been killed in a ***computer crash***,
But, when it happens, they wish they were dead.

NEW ELEMENT DISCOVERED: "Administratium"

Investigators at a major US research university recently discovered the heaviest element known to science. The element, tentatively named *administratium*, has no protons or electrons and thus has an atomic number of zero. However, it does have one neutron, 125 assistant neutrons, 75 vice neutrons and 211 assistant vice neutrons, thus yielding an atomic mass of 412.

These particles are held together by a force that involves the continuous exchange of meson-like particles called morons. It is also surrounded by vast quantities of lepton-like particles called peons. Since the element has no electrons, administratium is inert. However, it can be detected chemically—because it impedes every reaction it comes in contact with. According to researchers, a minute amount of administratium causes one reaction to take more than four days to complete what normally would have occurred in less than a second.

Administratium has a normal half-life of approximately three years at which time it does not decay, but rather undergoes a reorganization in which a portion of the assistant neutrons, vice neutrons and assistant vice neutrons exchange places. In fact, the mass of a sample of administratium actually increases over time, since, with each reorganization, some of the morons inevitably become neutrons, forming new isotopes. This characteristic of moron promotion has led some scientists to speculate that perhaps administratium is spontaneously formed wherever morons reach a certain critical concentration. This hypothetical quantity is referred to as "critical morass."

some "Useful Metric Conversions."

1 million microphones = 1 megaphone
2000 mockingbirds = two kilomockingbirds
10 cards = 1 decacards
1 millionth of a fish = 1 microfiche
453.6 graham crackers = 1 pound cake
1 trillion pins = 1 terrapin
10 rations = 1 decoration
100 rations = 1 C-ration
10 millipedes = 1 centipede
3 1/3 tridents = 1 decadent
2 monograms = 1 diagram
8 nickels = 2 paradigms
2 physicians in a golf cart = 1 paradox

...SCIENCE LITE

Medical terms of interest in certain parts of rural America:

Benign.....What you be, after you be eight
Artery.....The study of paintings
Bacteria.....Back door to cafeteria
Barium.....What doctors do when patients die
Cesarean Section.....A neighborhood in Rome
Cat scan.....Searching for a kitty
Cauterize .....Made eye contact with her
Colic.....A sheep dog
Coma.....A punctuation mark
D&C.....Where Washington is
Dilate.....To live long
Enema.....Not a friend
Fester.....Quicker than someone else
Fibula.....A small lie
Genital.....Non-Jewish person
G.I.Series.....World Series of military baseball
Hangnail.....What you hang your coat on
Impotent.....Distinguished, well known
Labor Pain.....Getting hurt at work
Medical Staff.....A Doctor's cane
Morbid.....A higher offer
Nitrates.....Cheaper than day rates
Node.....I knew it
Outpatient.....A person who has fainted
Pap Smear.....A fatherhood test
Pelvis.....Second cousin to Elvis
Post Operative.....A letter carrier
Recovery Room.....Place to do upholstery
Rectum.....Darn near killed him
Secretion.....Hiding something
Seizure.....A Roman emperor
Tablet.....A small table
Terminal Illness.....Getting sick at the airport
Tumor.....One plus one more
Urine.....Opposite of "you're out"

Great minds discuss ideas, Average minds discuss events, Small minds discuss people.

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"RNA interference" (RNAi)

The classical approach to assigning gene function in complex organisms is to inactivate the gene and see what happens. In a previous issue of ***Interface*** we described the exciting new technique called **RNAi**, whereby gene expression can be blocked via double-stranded RNA. This form of posttranslational gene silencing was first discovered in the roundworm *Caenorhabditis elegans* (and thought to be unique to this species) and then in the fruit fly *Drosophila melanogaster* [*Cell* **99:** 123, 1999; *Nature Biotechnol* **17:** 1158, 1999]. In a flurry of reports, the RNAi phenomenon has now been reported in plants, fungi, and mouse early embryos [*Nature Biotechnol* **17:** 1184, 1999; *Nature Cell Biol* **2:** 70, 2000; *Science* **287:** 2431, 2000] and, most recently, in zebrafish [*Dev Biol* **217:** 394, 2000]. As with most biological phenomena, if it occurs in one species it is likely to occur in many (or all) other species!

The CEG solicits applications for the Pilot Project Program awards which are given out each year. Are you interested in submitting a proposal relevant to environmental genetics or community outreach and education **????** if so please contact ***email: michelle.ginn@uc.edu phone: (513) 558-3625.***

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