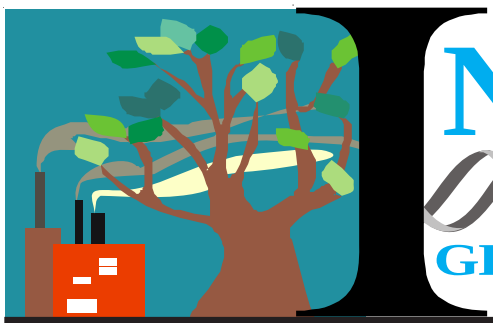
Issue Number 30



INTERFACE:
GENES AND THE ENVIRONMENT

CENTER FOR ENVIRONMENTAL GENETICS UNIVERSITY OF CINCINNATI SUMMER/FALL 05

Alavro Puga, PhD, Director **Daniel W Nebert, MD, Editor** Marian L Miller, PhD, Assistant Editor

Exposure to a Toxic Waste Dump Site: A True Story

The story you are about to read below is true. Only the names and locations have been changed to protect the innocent.

The early years

Having grown up in the same rural farming community, John and Martha began dating during their junior year. Both graduated in 1947 from the same high school. John went off to the State University to major in agriculture, but his father Orville became ill and could no longer handle all the chores around the Smith farm**;** therefore, John was forced to return home at the end of the first semester of his freshman year—in order to take over the farm responsibilities. There were cattle and chickens to feed, cows to milk, pigs to slop, eggs to gather, various animals to slaughter, and hay in the fields to mow. These duties took approximately 6-8 hours every day, 6 or 7 days a week.

Although she was a bit unhappy that John had not continued in college (in which case, he would have become the first from either side of the family to earn a college degree), Martha had to admit that she enjoyed John being back in town. They continued to see one another on dates every Saturday.

Environmental "bumps in the road" before getting hitched

At Christmas 1948, John and Martha became engaged and planned their wedding for the following June. Over the next several weeks, John began to experience extreme tiredness, intermittent fever, night sweats, loss of appetite, weight loss, headaches, and pain in the joints. He was diagnosed with *Bang's disease***;** this is also called *undulating fever* and the correct term is *brucellosis*. Anyone can get this, by being infected with bacteria from one of the *Brucella* species. Persons at highest risk are those who work with infected farm animals such as ranchers and veterinarians, and persons who consume raw milk (or products made from raw milk). In these early years of antibiotics, John's brucellosis was treated with chloromycetin and bed rest. Today, the antibiotics of choice include doxycycline and rifampin.

Although the Smith farm's cattle were infected with *Brucella*, which gave John his health problems, the situation was confounded by the concomitant diagnosis of "*X disease*" in the same cattle. This disorder was first described in summer of 1946 in

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Saskatchewan, the cause unknown. Usually just one or a few cows in a herd are affected, resulting in death between three and ten days. The acute form shows a sudden fever, eyes tearing, drooling, dehydration, and refusal to stand or eat. In later stages, there is blood in the stool and the abdomen becomes bloated. Post mortem findings include**:** ulcers of the mouth**;** denuded membranes in most of the gastrointestinal tract**;** no evidence anywhere of inflammation**;** and small hemorrhages in the kidney cortex, spleen, and peritoneal membranes. The subacute form shows similar but milder symptoms, with a thickening of skin and especially the mucous membranes (*hyperkeratosis*).

Recovering from Bang's disease and presuming that X disease in cattle was not related to his brucellosis, John was declared healthy enough in June 1949 to marry Martha—as planned.

Finding the etiology of X disease

Although X disease of cattle was believed to be caused by eating a toxic substance, in the 1940s the source was unknown. In 1954 the cause of this disorder was elucidated, in part, by the veterinarian Wilson Bell—who discovered, on a Virginia farm where this disease was prevalent, that cattle were licking the axles of farm machinery. Dr. Bell brought some of the lubricant on these axles back to his laboratory**;** he fed it experimentally to calves, and this produced the disease. It then became common knowledge that cattle can be poisoned by ethylene glycol, chlorinated naphthalene, various polycyclic aromatic hydrocarbons (**PAHs**) present in petroleum products, and other substances used in drilling and operating oil and gas wells. Cattle have been poisoned by a wide variety of chemical mixtures. The most common route-of-exposure is oral.

Exposure occurs when these materials are available to cattle, or when water and foodstuffs are contaminated. Cattle, as a leisure activity, apparently enjoy sniffing, licking and eating crude oil products**!** Based on morbidity patterns in cattle herds, the amount of toxic substance ingested is highly variable. When the material exists somewhere in the pasture, one or just a few cattle become ill. When water and foodstuffs are contaminated, a larger number or almost the entire herd generally is affected. For substances high in volatile hydrocarbons, the lung is a target organ. Hydrocarbons also affect the kidney, liver, immune system, and brain**;** exposure-linked abortions have also been reported in cattle. Diethylene glycol targets the brain, liver and kidney. The reported threshold dose of "fresh" oil for cattle ranges from 2.5 to 5.0 ml/kg body weight, whereas the reported threshold dose for weathered oil is 8.0 ml/kg.

Toxic waste dump site

Concerning X disease, farmers throughout the community tried hard to eliminate all farm machinery and other sources of oil, grease and petroleum from pastures in which their cattle fed. In the case of the Smith farm, however, a second source of environmental pollution loomed, of which they initially were unaware. Next to their property and sitting on higher ground was a dead-end road where—beginning about 1920—old refrigerators, stoves, batteries, transformers, and automobiles had begun increasingly to be deposited (this site became an official county dump in 1960 and remains so, to this day). A babbling brook ran through the Smith farm pasture, and John recalls fishing as a child and catching trout in the clean water. By 1950 the water was no longer clear, oil slicks could sometimes be seen, and all the trout had vanished.

John and Martha's growing family

Soon John and Martha were blessed with children**:** **A**lice was born in 1950, **B**enjamin in 1953, **C**arol in 1957, **D**ennis in 1959, and **E**llen arrived in 1962. The children all helped with the farm chores. In retrospect, "it seemed like the children were always sick with sore throats, ear infections and colds. Most family members were always tired and grouchy, but this was attributed simply to our family having increased, rather quickly, from two to seven members, plus all the work that needed to be done on our farm", said Mary.

In 1970 it was a local physician who first made the startling connection of "tiredness" with the environment. The father and four of the five children were all diagnosed with thyroid disease, and it was these five family members who had always drunk raw milk from the cows**;** Martha and her daughter Carol did not have thyroid disease and had avoided the milk. In contrast, all seven had always eaten cooked beef from their cattle and eggs from their chickens. In addition, Dennis developed protruding eyeballs (*exophthalmos*), another manifestation of his thyroid disease, and Alice was diagnosed with Addison's disease (failure of adrenal gland cortex to function). There is a common thread to all these

diseases**:** they are the result of *endocrine disruption***;** hence, these disorders are now known to be caused by chemicals called *endocrine disruptors*.

John and the four children with thyroid disease were also found to have abnormally low lymphocyte counts (termed "*lymphocytopenia*")**;** this is a manifestation of suppression of the immune system. The physician explained to John that his family members "apparently have a gene, which is normally latent in the general population, but can cause disease if stimulated by a certain environmental signal". What could the environmental stimulus be, and was the source of these illnesses the milk from their cows?

Turning to legal issues

John collected water and mud sediment from the stream in his pasture. Analysis by a local chemical laboratory determined the existence of high levels of polychlorinated biphenyls (**PCBs**), PAHs and other petroleum products, mercury, and detectable levels of the cancer-causing metals chromium, cadmium, and nickel. In 1980 the two youngest children were also evaluated by a university hospital in the nearest large city**;** nothing new was uncovered.

John and Martha, of course, were outraged. For decades, a toxic waste dump site was leaching numerous chemicals into their pasture, the cows were eating the grass and drinking water from the contaminated creek, and the family was slowly being poisoned by drinking milk from these cows. (Most of the Smith farm milk was sold to a local company, which then processed large amounts of dairy products**;** presumably, the contaminated milk from their farm was sufficiently diluted by good milk from dozens of other farms—so that the entire community did not develop these environmental diseases**!**)

A lawsuit, seeking medical damages to the five Smith family members, was submitted to the nearby town, but this was denied because the "dump site" was several miles beyond the "boundaries of the town". A long battle ensued, between John and the County government**;** after years of wrangling, several lawsuits were again unsuccessful. The same thing happened when John appealed to the State government. John became aware that "the County had some kind of insurance policy to pay for these kinds of environmental damage" (or to pay for lawyers to prevent the County from having to pay). After "losing about $120,000 in their various attempts to sue", John and Martha gave up. The County and State governments also sent the family an official mandate**:** "Do not test water on or near your property, ever again".

Fast-forward to the present

Today, all five children have married, with one getting a divorce and remarrying. The three daughters, at least, are beyond or now approaching the end of their child-bearing years. Carol (the child who did not drink the raw milk) has three children. The other four are childless**;** John and Martha feel quite certain that all of them "tried to have babies". Infertility is therefore presumed to exist. Except for one of the four, the other three children were never evaluated medically for infertility.

Conclusions

The Leading Article in the previous issue discussed *toxic waste production* in the U.S.**;** it is estimated to range between 10 million and 2.9 billion tons per year, or roughly 100 to 2,500 pounds per year for each man, woman and child in the country. The Office of Technology Assessment (**OTA**) has concluded that there are probably *upwards of 500,000 chemically-contaminated sites* in the U.S. This means there is always the possibility (indeed, the likelihood) that what goes into the ground will return to cause environmental diseases—including thyroid and adrenal disease, infertility, suppression of the immune system, birth defects, nervous system injury, skin disorders, kidney and liver diseases, blood disorders, and cancer.

The family described in this Leading Article suffered from endocrine disruption in the form of thyroid disease, adrenal insufficiency, and apparent infertility. It is likely they also had suppression of the immune system (which could account for so many colds, sore throats and ear infections). As detailed in the Leading Article in our previous issue, toxic waste dump sites notoriously contain *complex mixtures* of chemicals and metals**;** thus, one single causative agent is virtually never possible to prove. For example, with endocrine disruption, dioxin-like compounds, PCBs, phthalates, arsenic, and cadmium (among others) are all environmental toxicants known to cause endocrine disruption. The Smith family has suffered a double-whammy**:** not only has this family been plagued over at least two generations with these environmental problems, but the legal system is set up in such a way that they cannot successfully convince local or State governments that they should be

compensated for their medical costs, injuries and anguish over several decades.

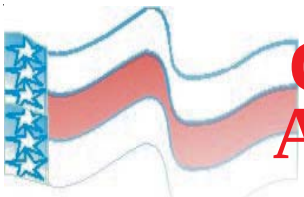
Much work is needed in order for us to understand how to quantify the effects of two or more environmental agents on the cell, the tissue, and the intact animal or patient. Multiple effects by each chemical or metal might act additively, or be synergistic or inhibitory, on various critical life processes, in ways that are virtually impossible to predict. The effects of complex mixtures will confound any attempts at human risk assessment concerning materials present in toxic waste dump sites. New experimental paradigms are needed. In this true story, for example, how can an environmental scientist ever hope to determine the amount of exposure, the duration of exposure, and how all the chemicals and metals to which they were exposed contributed to their diseases?

Concerning ethical, legal and social issues—this Leading Article also underscores the problems and deficiencies. The U.S. citizen usually remains a victim to governmental laws and regulations about environmental contamination. The citizen does have a legal chance, if it can be proven that the toxic waste dump site has been generated specifically by one chemical company. To try to sue local or State governments, however, is extremely problematic. How many hundreds or thousands of other families around the world have suffered, knowingly or unknowingly, over the past century, or are suffering today, due to similar predicaments concerning hazardous waste dump sites?

—contributed by Dan Nebert

All gene names (human and animal)--in this and all issues of *Interface* can be found at

http://www.gene.ucl.ac.uk/nomenclatature/



Only in America.....

...do banks leave both doors open and then chain the pens to the counters.

Latest in Genetics and Genomics, ...

What follows is a synopsis of some of the more interesting things that have happened during the last 6 months of 2005 with the Human Genome Project (**HGP**), and related genetics/genomics news, provided chronologically**:**

Jul 2005 *Leishmania* is a parasite that causes a spectrum of human diseases. The *Leishmania major* genome has now been sequenced [*Science* 2005; **309:** 436]. The 32.8-million-base (**Mb**) genome has 911 predicted RNA genes and 8,272 putatively functional protein-coding genes.

RNA interference (**RNAi**) works by tiny microRNAs (~22 nucleotides in length) that can bind mRNA of certain genes and block their expression. At first believed to be quite rare, the latest findings now are that the total number of human genes encoding miRNAs is at least 800 and perhaps several thousand [*Nat Genet* 2005; **37:** 766].

Aug 2005 A map-based high-quality finished sequence covering 95% of the 389 Mb of **the rice genome** has been completed [*Nature* 2005; **436:** 793]. Almost one-third of the 37,544 putative protein-coding genes appear in clustered gene families. About 2,859 genes appear to be unique to rice and other grains. Why rice and other plants appear to have more genes than humans—remains an intriguing question.

Sep 2005 The number of nucleotide bases in the world's three major DNA-sequence databases—in GenBank (U.S.), European Bioinformatics Institute (U.K.), and DNA Data Bank (Japan)—topped **100 billion** this month. The three databases have been doubling in size every 14 months, actually growing faster than our computing capacity**..!**

Oct 2005 Phase I of the **HapMap** Project is now considered completed. More than 1.1 million single nucleotide polymorphisms (SNPs) have been genotyped in **270 individuals** from four worldwide populations [30 sets of two parents and child (**trio**) from Yoruba, Nigeria; 30 trios from Northern Europeans; 45 unrelated Japanese from Tokyo area; and 45 unrelated Chinese from Beijing area]. Data are available at http://www.hapmap.org.

Nov 2005 The accepted dogma is that one DNA segment, associated with another contiguous DNA segment, is in linkage disequilibrium (**LD**). Evidence is increasingly clear, however, that clusters of SNPs on one DNA segment can be in LD with another cluster—hundreds of kilobases away and, indeed, even on other chromosomes [*Genome Res* 2005; **15:** 1503]**..!** This realization should help us understand better phenotype-genotype association studies of human complex diseases.

For quantitative trait loci (**QTL**) mapping, outbred stocks of mice (which more closely resemble human populations) are shown why they have distinct advantages over highly inbred mouse lines [*Nat Genet* 2005; **37:** 1181].

For years, many have discussed the likelihood that the same transcription factor can up-regulate one gene, while down-regulating another. The transcription factor KLF4 is the latest example [*Nat Cell Biol* 2005; **7:** 1074]. KLF4 induces the *CDKN1A* gene (which controls normal cell proliferation) while suppressing the *TP53* gene (which suppresses tumor growth). In many tumors, KLF4 becomes a growth promoter when *CDKN1A* is not functioning, and KLF4's suppression of *TP53* goes unchecked.

Dec 2005 Joining the mammalian genomes of the human, mouse and rat, a high-quality draft genome sequence of the **domestic dog** (*Canis familiaris*), together with a dense map of SNPs across many breeds, has now been published [*Nature* 2005; **438:** 803].

The genomes of **three fungi—**the model organism *Aspergillus nidulans*, a serious human pathogen *A. fumigatus*, and *A. oryzae* used in the production of sake, miso and soy sauce—have been sequenced and compared with one another [*Nature* 2005; **438:** 1105].

It is well known that one can slice up flatworms into tiny pieces, and the pieces are able to regenerate an entire planarian flatworm. If just one gene is blocked, however [*Science* 2005; **310:** 1327], this remarkable ability is lost. It was concluded that the *smedwi-2* gene (which has counterparts in many other species) might be part of a universal regulatory mechanism for regeneration based on stem cells.

Almost 300 bacterial genomes have now been sequenced [*Genome Res* 2005; **15:** 1603]. Comparing all these genomes is leading to everything—from understanding basic biological processes, host-pathogen interactions, and protein-protein interactions—to discovering DNA variations that can be used in genotyping or forensic analyses, design of novel antimicrobial compounds and vaccines, and the engineering of microbes for industrial applications.

Best Typo

1024x768 pikels per inch

Evolutionarily Speaking,...

What follows is a synopsis of some of the more interesting things that have happened during the last 6 months of 2005 with **evolutionarily-related** news, provided chronologically**:**

Jul 2005 Comparing 13,731 annotated protein-coding genes from **humans** to their **chimpanzee** counterparts (**orthologs**) [*PLoS Biol* 2005; **3:** e170], evolutionary changes that leave a noticeable signature throughout the genome were searched for. The strongest signatures of positive selection were found in the gene categories of tumor suppression, apoptosis (**cell death**) and especially spermatogenesis.

Another study of 49 patients and their families [*Am J Hum Genet* 2005; **76:** 1074] has shown a variety of mutations in the *FOXP2* gene, which are responsible for *dyspraxia* (difficulty in articulating speech). As we have reported in earlier issues of ***Interface***, other primates have the same *FOXP2* mutations as humans who cannot speak, which might be why apes cannot articulate speech like humans can.

Aug 2005 Genomes include *transposons*, little segments of DNA that jump between chromosomes and don't belong there. One particular transposon was found in fruit flies to be associated with insecticide resistance [*Science* 2005; **309:** 764]. It turns out that this transposon inserted itself into an "insecticide sensitivity" gene ~90,000 years ago and with the introduction of insecticides during the 20th century, the fact that this transposon had knocked out this gene has led to a selective advantage for this subset of fruit flies**..!**

Sep 2005 New evidence was reported that evolution of the human brain did not stop when humans diverged from chimpanzees about 5-6 million years ago [*Science* 2005; **309:** 1717 & 1720]. A major difference between humans and chimps is brain size. Two human genes [microcephalin (*MCPH1*) & abnormal spindle-like, microcephaly-associated (*ASPM*)] responsible for mental retardation and *microcephaly* (**small brain**) in children have been shown to have the same mutated base pairs that still exist in the chimpanzee.

Oct 2005 Discovery of a single partial skeleton in Flores (the southeastern tip of Indonesia) has excited many scientists because the tiny adult fossil was no more than a meter tall and dated to 18,000 years ago. They proposed a new species, *Homo floresiensis* [*Nature* 2005; **437:** 1012]. The brain volume is roughly the size of that of a chimpanzee, and the tiny species had longer-than-normal arms. Previous studies had determined that *Homo erectus* arrived on Flores at least 800,000 years ago, and it is proposed that *H. floresiensis* evolved from *H. erectus* through dwarfing.

Old textbooks say that protein-coding genes evolve through time, while the DNA between genes (so-called "junk" DNA) does not. Lining up two fruit fly genomes (*Drosophila melanogaster* and *D. simulans*), Andolfatto found that much of their non-coding DNA shows divergence and evolution, suggesting that a large fraction of the non-coding DNA might be functionally important and subject to both purifying selection and adaptive evolution [*Nature* 2005; **437:** 1149].

Once in a great while, mRNA is reverse-transcribed to cDNA, then inserted back into a chromosome (usually different from the one on which its parent gene resides). This "*retro-pseudogene*" remains useless, but occasionally (by unknown mechanisms) a promoter is recruited and the gene becomes functional and fixed into the organism's genome. On average, the estimate [*PLoS Biol* 2005; **3:** 399] is that one such gene arises every one million years in several mammalian species.

Nov 2005 The retinoblastoma gene (*RB1*) in humans and other mammals has a related gene (an *ortholog*) in plants, called retinoblastoma-related (*RBR*). The gene product RBR gene is important in WNT-signaling pathways involving root development in plants [*Cell* 2005; **123:** 1337].

Dec 2005 The **2005 Breakthrough of the Year**, as chosen by *Science* magazine, is "**evolution in action**." The number of publications and new findings about evolution has exploded during 2005. Being able this year to compare the human and chimpanzee genomes, two sea squirt genomes, two fruit fly genomes, or several viral genomes, researchers have made major advances in pinning down the **molecular modifications that have driven, and continue to drive, evolutionary change..!**

Biotechnology, ...

Tidbits during the last half of 2005, concerning genetically-modified (**GM**) plants, biotechology, and related topics**:**

Jul 2005 British researchers [*Nature* 2005; **436:** 453] have found that **GM** oilseed rape is able to interbreed with charlock, a related wild-weed species. The 3-year study did not find evidence, however, that herbicide tolerance is spreading to these weeds.

African trypanosomes are parasites that cause sleeping sickness in humans. The genome of *Trypanosoma brucei* has been sequenced [*Science* 2005; **309:** 416]. The 26-million base (**Mb**) genome contains 9,068 predicted genes, including ~806 variant surface glycoprotein genes used by the parasite to evade the immune system of humans and other mammals.

Aug 2005 There continue to be fears that genes from **GM** food might transfer to domestic food plants and weeds. From hundreds of corn plants from 125 fields sampled in 2003 and 2004 in Oaxaca, Mexico [*PNAS* 2005; **102:** 12338], 153,000 seeds showed **no** transgenes coming from **GM** corn planted nearby.

Olestra is a non-absorbable fat substitute, approved by the FDA in 1996 for decreasing one's uptake of cholesterol and fats from the intestine. Now it appears that olestra might be a way to rid the body of toxicants such as dioxin and polychlorinated biphenyls (**PCBs**) [*Environ Health Perspect* 2005; **113:** A518].

Sep 2005 In the laboratory of this Editor between 1982 and 1986, several postdoctoral fellows were able to sequence between **6 and 1,000 bases**

in a week. Now, a new system is reported [*Nature* 2005; **437:** 376] that can read 25 million base pairs of DNA in 4 hours**;** some problems still remain, but this new technique looks very promising.

A "universal mating hormone" has been identified from *Phytophthora*, a fungus responsible for potato blight and sudden death in oak trees [*Science* 2005; **309:** 1828]. Intriguingly, the 20-carbon chemical structure looks very similar to that of mammalian eicosanoids (small molecules important in virtually all critical life processes.

Oct 2005 Transgenic crops that produce a toxin from *Bacillus thuringiensis* (**Bt**) can show resistance against certain insect pests and thus decrease their reliance on insecticides. Many are concerned, however, that usefulness of Bt toxins would be cut short by the rapid evolution of resistance in insect pests. Pink bollworm resistance to Bt toxin was monitored in an Arizona cotton field for 8 years, and no net increase from 1997 to 2004 was found in the mean frequency of pink bollworm resistance to Bt toxin [*PNAS* 2005; **102:** 15389]. This represents more good news for **GM** plant research.

The mouse *Prox1* gene is required for the formation of lymphatic endothelial cells. *Prox1(-/-)* knockout mice became progressively obese [*Nat Genet* 2005; **37:** 1072], suggesting for the first time a link between our lymphatic system and obesity**..!**

Nov 2005 Of the more than 13,000 genes that make up the genome of the coffee plant *Coffea canephora*, almost all of the genes have counterparts that perform the same function in the genome of the tomato plant *Solanum lycopersicum* [*Nature* 2005; **438:** 398]. Such a close relationship between coffee and tomato plants had not been previously appreciated.

Dec 2005 Using large-scale empirical and simulated data sets [*Nat Genet* 2005; **37:** 1320], it was found that the sample sizes used in **the HapMap Project** are sufficient to capture common DNA variant sites, but that performance declines substantially for variants having minor allele frequencies of less than 5%.

A new technique is demonstrated [*Genomics* 2005; **86:** 759] that can very quickly resolve all DNA variants located on a stretch of DNA 400,000 bases (**400 kb**) long (or longer) on each of the two chromosomes (*i.e.* haplotypes) of multiple individuals.

Aminoglycoside antibiotic-induced hearing loss

Aminoglycoside antibiotic-induced hearing loss is a well-known pharmacogenetic disorder. Some patients being treated with an antibiotic develop hearing loss, whereas many others receiving the same dose of the drug do not. Drugs that kill gram-negative bacteria (*e.g.* gentamycin, otomycin, kanamycin, amikacin, tobramycin, sisomicin and netilmicin) are especially prone to cause this pharmacogenetic disorder. Mutations in certain mitochondrial genes have been demonstrated to contribute to this susceptibility trait.

L-carnitine is an effective treatment for preventing this hearing loss. Gentamycin induces cell death (*apoptosis*) of auditory cells by an ERK1/ERK2-mediated pathway through the up-regulation of the *Harakiri* (***HRK***) gene. HRK up-regulation is crucial for gentamycin-induced apoptosis, and this can be prevented by *L*-carnitine which acts by means of the c-Jun N-terminal kinase (**JNK**). This breakthrough [*PNAS* 2005; **102:** 16019] could shed some light on the mechanism of this pharmacogenetic disorder.

"Q"uote of the month

Give me the benefit of your convictions, if you have any, but keep your doubts to yourself, for I have enough of my own.

Johann Wolfgang von Goethe, *1749-1832*

Ethical, Legal and Social Issues, ...

ELSI tidbits from the last 6 months of 2005**:**

Jul 2005 Between 40% and 80% of variation in the human intelligence quotient (**IQ**) is attributable to genetic factors. A genome-wide scan [*Am J Hum Genet* 2005; **77:** 318] showed linkage on chromosomes 2q (a region that has been associated with autism) and 6p (region associated with reading and learning disabilities).

Sexual preference has an environmental and a substantial genetic component. Because of previous studies showing linkage of male orientation to markers on the X chromosome, X chromosome inactivation ratios in 97 mothers of homosexual men were compared with 103 age-matched control women without gay sons. The number of women with extreme skewing of X-inactivation was significantly higher in mothers of gay men (13%) compared to controls (4%), and was increased in mothers with two or more gay sons (23%), supporting a role for the X chromosome in the cause of male homosexuality [*Hum Genet* 2005; **118:** 691].

Aug 2005 The Kansas Board of Education has voted to allow for "the teaching of alternatives to evolution" [*Science* 2005; **309:** 1163]. By highlighting gaps in current scientific thinking, once again these lay people are attempting to slip "Intelligent Design" into the academic curriculum.

Teenagers, especially overweight children, who are exposed to cigarette smoke, have been shown to be at increased risk of the metabolic syndrome [*Circulation* 2005; **112:** 862]. The metabolic syndrome predicts future coronary artery disease and type II diabetes and often begins to emerge during childhood.

Sep 2005 Large pharmaceutical companies are moving rapidly to acquire biotechnology companies—especially if the price is reasonably low [*Nature* 2005; **437:** 475].

During the era when nuclear bomb testing was rampant (1955-1963), the amount of radiocarbon present in tooth enamel is a remarkably accurate indicator of when a person was born [*Nature* 2005; **437:** 333]. Age in those born during 1955-63 could be determined with 1.6 years, whereas the commonly used morphological evaluation of skeletal remains and tooth wear is sensitive to only 5-10 years for adults**..!**

Oct 2005 Pathological (or compulsive) liars have been found to have ~25% more white matter in the prefrontal cortex [*Br J Psychiatry* 2005; **187:** 320]. White matter presumably implies "more neural connectivity," which might facilitate lying—suggesting that a lie might be "harder to do than tell the truth"**..!**

Nov 2005 Adding mitochondria from the egg of a second woman during in vitro fertilization is thought to boost egg development and correct certain inherited diseases involving mitochondrial defects [*Nature* 2005; **437:** 305]. Creating mice having mitochondria from two mothers [*Nature* 2005; **438:** 12], however, the Doug Wallace lab found that offspring with swapped mitochondrial DNA had a greater likelihood of infertility and fewer numbers of viable newborns. Ethical concerns, therefore, remain about babies derived from two mothers and one father.

Everyone knows that males and females often respond differently in perceiving humor in jokes or cartoons. Using event-related functional magnetic resonance imaging (**fMRI**), differences in "humor-response" effects in several regions of the brain were demonstrated between men and women [*PNAS* 2005; **102:** 16496].

A biological anthropology team recruited 66 bachelors, 30 married men without children, and 30 married fathers in Beijing**;** all were between 21 and 38 years of age. Compared with bachelors, childless husbands showed 20% lower levels of testosterone (testing saliva in the morning when this hormone is the highest), and married fathers had ~50% lower levels [*Science* 2005; **310:** 1114]. Next, the team plans to see if higher testosterone levels are associated with poorer male-parenting skills**..!**

Dec 2005 Because a large fraction (more than half) of Americans "do not believe in evolution," David Sloan Wilson provides a fascinating essay [*PLoS Biol* 2005; **3:** e364] on a success story—as to how to develop a single college course or university-wide program called "**EvoS**." Enthusiasm from college freshmen to senior administrators proves that it IS possible to present all the evidence to a class of doubters and have them change their minds into accepting evolution.

Gene-Environment Tidbits of Interest

Jul 2005 Blood lead (**Pb**) levels above 10 µg/dL are known to cause intellectual impairment. Now comes a report from CEG member **Lanphear** and colleagues [*Environ Health Perspect* 2005; **113:** 894], collecting data from 1,333 children in several countries, showing intellectual deficits can be seen in children having blood Pb levels of even less than 7.5 µg/dL**..!**

In a recent review of 2,050 quantitative-trait loci (**QTL**) that had been mapped in various inbred mouse strains [*Nat Rev Genet* 2005; **6:** 271], only 15 have been "cloned and characterized to the point of proving plausible gene variation and causation" in mice and human populations**..!** Hence, QTL mapping is all well and good, but the yield of success has been very low—at least, so far.

Aug 2005 An epidemiological team in Canada has found that even low-level chronic exposures to some endocrine disruptors (*e.g.* polychlorinated biphenyls; **PCBs**) can alter thyroid hormone status and decrease chances of pregnancy [*Environ Health Perspect* 2005; **113:** 1039]. This study is consistent with the real-life stories presented in the Leading Article of this issue.

Scientists have discovered a gene that controls the speed at which patients develop tuberculosis [*PNAS* 2005; **102:** 12183]. The gene (official name *SLC11A1*) encodes NRAMP1, which is a divalent cation transporter and probably moves zinc into cells—which is important in battling many inflammatory processes.

Sep 2005 Toxicity of the heart caused by dioxin was tested during chick development in the egg. Plymouth Rock-Barred chick embryos were found to be 4-5 times more sensitive than White Leghorn-Babcock chick embryos [*Toxicol Appl Pharmacol*2005; **167:** 210], but the mechanism for this strain difference has not yet been elucidated.

Oct 2005 The determination of *serum osteopontin levels* appears to be the most reliable test yet, to identify workers who have had varying degrees of exposure to **asbestos**—many of the workers having asbestosis, benign pleural lesions, or both [*New Engl J Med* 2005; **353:** 1564].

Putting a breast cancer model into a variety of inbred mouse strains [*Nat Genet* 2005; **37:** 1026] produced a large spectrum in the rate of *metastasis* (spreading of cancer cells to other organs). These studies suggest that the propensity for metastatic cancer is a genetic trait in mice, and this is likely to be also true in humans.

From a PCB-contaminated population in eastern Slovakia [*Environ Health Perspect* 2005; **113:** 1277], the study suggested dioxin-like PCBs might be responsible for a weak anti-estrogenic effect in male serum. This is yet-another study related to this issue's Leading Article.

Nov 2005 Dioxins are known to cause birth defects, suppression of the immune system, tumor promotion, and sex hormone action. All of these effects are mediated by the aryl hydrocarbon receptor (**AHR**). A possible mechanism was suggested for the toxic effects of dioxins and other AHR ligands as endocrine disruptors [*Mol Cell Biol* 2005; **25:** 10040].

Over a 4-day period, young female rats were exposed to six different doses of a halogenated mixture of 2 dioxin-like compounds, 4 dibenzofurans, and 12 PCBs [*Environ Health Perspect* 2005; **113:** 1549]. Effects on the thyroid hormone **T4** (thyroxine) were seen at doses of these chemicals at least an order of magnitude below their known effective doses. Again, this publication explains what might be happening in the affected family described in the Leading Article of this issue.

Uterine leiomyomas (**fibroids**) are common benign tumors in the muscular wall of the uterus and occur in as many as three-fourths of women. Diethylstilbestrol was found [*PNAS* 2005; **102:** 8644] not to cause a mutation in estogen-responsive genes, but rather to cause them to become "reprogrammed" so that they responded differently to normal estrogen stimulation later in life. This "reprogramming" process is called *imprinting.*

Cadmium is a toxic metal, taken into our bodies primarily in cigarette smoke and contaminated foods, especially shellfish. Cadmium is known to be absorbed in the lung and intestine and sequestered in the kidneys. In a large Swedish population [*Environ Health Perspect* 2005; **113:** 1627], the lowest-observed-effect level for causing kidney damage was 0.6 µg per liter of urinary cadmium—considerably lower than previously reported levels.

Dec 2005 Cigarette smoke extract inhibits yeast growth and causes many changes in gene expression that span many functional classes of yeast

genes [*BBRC* 2005; **338:** 1578]. This is not particularly surprising, because benzo[*a*]pyrene, a prototypical chemical in cigarette smoke, has been known for decades to up-regulate many genes in plants, as well as in animals.

Lithium is used clinically to treat certain psychiatric conditions. Now comes a study showing that lithium in mice enhances bone formation and improves bone mass, via the WNT-signaling pathway [*PNAS* 2005; **102:** 17406]. Could similar effects be happening in humans?

Congratulations

Interface: ***Genes and the Environment***

The NIEHS Community Outreach Resource Center Board-- continuously receives new materials. We were notified that website has received 2,807 hits and 983 outreach materials have been downloaded. The **Top Ten** most downloaded materials for January and February are as follows:

1. ***Interface: Genes and the Environment*****, Issue No. 26** (PDF, 54 downloads) University of Cincinnati Center for Environmental Genetics COEP. The title of the article is

"Cigarette smoking: The Good, the Bad and the Ugly"

Graduate students say the darndest things

brunted
chromome
endoplasmic reculum
frip frop
phage contrast (phase contrast)

Human Variation, Disease, Migration and Evolution, ...

Tidbits on these topics from the last half of 2005**:**

Jul 2005 Compared with ~25,000 protein-coding genes, the human genome likely has several thousand micro-RNA (***miRNA***) genes, which encode RNA that binds to mRNA from various protein-coding genes, thereby regulating them. It was not surprising, therefore, in 173 *pre-miRNA* genes from 96 subjects [*BBRC* 2005; **331:** 1439] to find variant sites in these *miRNA* genes (having final products of 22 nucleotides), some of which exert profound effects**;** this represents yet one more problem of the "equivocal genotype" [*Eur J Pharmacol* 2004; **500:** 267].

Patients with lung cancer who get better with gefitinib (a drug used to treat cancer) therapy are reported to have mutations in their epidermal growth factor receptor (*EGFR*) gene [*N Engl J Med* 2004; **350:** 2129 & *NEJM* 2005; **352:** 786 & *PLoS Med* 2005; **2:** e73]. However, these three articles, plus two more [*NEJM* 2005; **353:** 207 & 208], show some patients who get better on gefitinib do not have the mutations and some who do not get better have the mutations. Such are the problems with pharmacogenomics and individualized drug therapy in 100% of any physician's patients**..!**

Aug 2005 The fishy odor of urine is a characteristic of a disorder called trimethylaminuria in humans, resulting from mutations in the flavin-containing monooxygenase-3 (*FMO3*) gene. A fishy flavor in cow's milk has been shown to be also caused by mutations in the cow *FMO3* gene. Now comes a study of a fishy flavor in chicken eggs**;** yep, again it's caused by *FMO3* gene mutations [*Genomics* 2005; **86:** 225].

Researchers have found a regulatory molecule that is involved in faulty dopamine signaling in the brain, and which breaks down in people who suffer depression [*Cell* 2005; **122:** 275]. Prostate apoptosis response-4, encoded by the *PAWR* gene, is produced in the same neurons where D2 receptors function. The PAWR gene might therefore be a possible target for designing drugs to treat depression.

Sep 2005 The trait of obesity has been linked in several population studies to the glutamate decarboxylase (*GAD2*) gene on chromosome 10.

Now comes a study [*PLoS Biol* 2005; **3:** e315 & e321] showing **a lack** of correlation. This study shows the importance, or the need, to corroborate every phenotype-genotype association finding in at least one additional ethnically different population—before it can be accepted as the truth.

Fourteen genes were studied in 470 Caucasian families, having one or more members with **autism** [*Am J Hum Genet* 2005; **77:** 377]. A γ-aminobutyric acid (**GABA**) receptor gene *GABRA4* was found to be involved in the origin of autism, and gene-gene interaction of *GABRA4* with *GABRB1* appears to increase risk of autism. In the human genome, there are 19 functional *GABR* genes.

Oct 2005 Studying 174 unrelated patients with Tourette's syndrome, a neuropsychiatric disorder having vocal and motor tics, variant sites in the *SLITRK1* gene (encoding a nerve-cell tyrosine kinase receptor) were found to be associated with the syndrome, whereas 3,600 control chromosomes did not show these mutations [*Science* 2005; **310:** 317].

For myocardial infarction (**MI**; heart attack), it is believed that more than 500 genes—perhaps in varying combinations—can contribute to this complex disease. A huge study of 11,053 single-nucleotide polymorphisms (**SNPs**) in 6,891 genes in three populations (340 cases, 346 controls; 445 cases, 606 controls; 560 cases, 891 controls) discovered four genes associated with MI**:** *PALLD, ROS1, TAS2R50* and *OR13G1* [*Am J Hum Genet* 2005; **77:** 596].

Nov 2005 Some people respond to glucocorticoid (**GC**) inhalers and their asthma improves, while others do not respond. The Icelandic company **deCODE genetics, Inc.** has uncovered a gene expression profile by selecting asthma patients from among their database of more than 7,000 *[PNAS* 2005; **102:** 14789]. Eleven of 15 genes predicted GC sensitivity with 84% accuracy, and one gene alone predicted clinical response with 81% accuracy.

Dec 2005 Pigmentation in humans reflects the number, size and density of melanosomes, which are the pigmented small bodies in skin cells (melanocytes). Starting with zebrafish wild-type versus *golden* mutants [*Science* 2005; **310:** 1782], Lamason and 24 coauthors found a mutation in the *slc24a5* gene responsible for differences in pigmentation of the fish. Extrapolating to the human

I used to have a handle on life, but it broke.

SLC24A5 gene, they found the evolutionarily conserved ancestral allele predominates in African and East Asian populations, whereas the variant allele occurs in light-skinned European populations. The human genes now known to participate in skin color include *SLC24A5*, *SLC45A2*, *ASIP*, *MC1R*, *OCA2*, and *TRP1*.

Some people are more susceptible than others to lung cancer, and the genes involved remain elusive. A recent study [*Nat Genet* 2005; **37:** 1315] found that a Thr790Met mutation in the *EGFR* gene, known to be involved in acquired drug resistance by lung tumors, occurred in an extended family having multiple cases of non-small-cell lung cancer.

The origin of farming in Asia and dispersal to Europe during the past 10,000 years is a fascinating topic. Using radiocarbon dates from 735 Neolithic sites in Europe and the Near East [*PLoS Biol* 2005; **3:** e410 & e436], the average rate of spread of farming westward and northward was estimated at 0.6 to 1.3 km per year—which is in close agreement with sociological measures of tribe migrations.

By fossil data, Asia's earliest evidence of hominids (early ancestors to modern-day humans) now dates back to 1,800,000 years ago [*Nature* 2005; **438:** 1099]. There is a growing consensus that there were two or more "waves" of migration out of Africa, the latest and most successful occurring between 45,000 and 65,000 years ago**;** a small amount of interbreeding (outside Africa) between "earlier" and "later" humans cannot be ruled out.

WHY IS AN ATHEIST ABLE TO GET INSURANCE AGAINST "ACTS OF GOD"?

LETTERS TO THE EDITOR

RESPONSES/COMMENTS TO VARIOUS QUESTIONS

Q My mother has age-related macular degeneration, which is a leading cause of blindness in people over age 75 in this country. I read in the newspaper that patients with this disease were studied with DNA chips, and a gene was found, "out-of-the-blue", which might aid in treating this terrible problem in the elderly. Can you give me any details about that study?

A *Yes, the article to which I think you are referring is* ***Science*** *2005; 308: 385. Using DNA chips having 100,000 variant sites, Klein and coworkers compared 96 people with age-related macular degeneration (**AMD**) with 50 healthy controls, in what is called a genome-wide association study. The scan found a gene (**CFH**) encoding complement factor H, which was mutated in AMD patients. CFH plays a role in the immune response; this finding is intriguing, because AMD is believed by many to be associated with inflammation of the retina of the eye. This study might be the first successful genome-wide analysis (**GWA**), done on such a grand scale. The only cautionary note is that the CFH gene is one major gene contributing (10% to 35%?) to AMD, and the many other major genes and modifier genes that also contribute to this disorder remain to be discovered.*

COMMENT **In the last issue [Observations by a Biologist], the fly *fruitless* (*fru*) gene was discussed in the context of male homosexuality in *Drosophila*. Kimura et al. [*Nature* 2005; 438: 229] have now shown that the *fru* gene product FRU supports the development of nerve cells with male-specific dendritic fields, which are programmed to die during female brain development (because of the absence of FRU). FRU expression therefore can produce a male-specific neural circuit by preventing cell death in identifiable neurons, and this circuit is probably used during heterosexual courtship.**

Q Concerning "multiple chemical sensitivity," have any genes that code for metabolism enzymes, that break down foreign chemicals in our environment, been studied—to see if there is any association between these genes and this common disorder?

A *Multiple chemical sensitivity (**MCS**) is also called idiopathic environmental intolerance (**IEI**). The current consensus for establishing the diagnosis of IEI requires that the patient satisfies six essential criteria: (1) reproducible symptoms with repeated exposures to chemical irritants; (2) it is a chronic condition; (3) later manifestation of symptoms occur at levels of exposure that are lower than previously tolerated; (4) improvement or complete cure can occur upon avoidance of the irritant(s); (5) similar symptoms happen when exposed to multiple chemically-related substances; and (6) multiple-organ symptoms (e.g. runny nose, itchy eyes, headache, scratchy throat, ear ache, scalp pain, mental confusion or sleepiness, palpitations of the heart, upset stomach, nausea and/or diarrhea, abdominal cramping, aching joints, etc.).* ***Interface*** *had a Leading Article on IEI in Issue **#22** (summer/fall 2001).*

*Are metabolism genes associated with IEI..? One such recent article [**Int J Epidemiol** 2004; 33: 971] looked at DNA variant sites in six genes: CYP2D6, NAT1, NAT2, PON1, PON2, and MTHFR. A gene-gene interaction between CYP2D6 and NAT2 suggested that rapid metabolism for both enzymes might confer ~18-fold greater risk for MCS. This demonstration needs to be replicated in a second population, however, before we can get excited about these findings.*

COMMENT **For decades, garlic has been touted as a drug to fight high blood pressure. Now there is molecular proof [*PNAS* 2005; 102: 12248]. The active ingredient is *allicin*, which excites the ion channel gene *TRPA1*, leading to release of peptides that mediate vasodilation. This, in turn, relaxes blood vessels and lowers blood pressure. TRPA1 has previously been identified as the target for spicy foods such as wasabi, yellow mustard, and chili peppers—suggesting that all these spices activate a common pathway.**

Observations by a Biologist

Management of warfarin therapy can be helped by genetic test

Warfarin is an *anticoagulant drug* that prevents our blood from clotting. Too much warfarin can lead to internal bleeding and even death. Too little warfarin can lead to formation of unwanted clots, which is the reason why a physician would want to give this drug in the first place.

In summer 2005 it was reported that the management of warfarin therapy is complicated by a wide *genetic variation in drug response* between patients. Variants in the gene encoding vitamin K epoxide reductase complex-1 (***VKORC1***) were found to affect the response to warfarin. A retrospective study of patients receiving long-term warfarin maintenance therapy yielded DNA that could be tested for single-nucleotide polymorphisms (**SNPs**). Multiple linear-regression analysis was able to determine the effect of *VKORC1* haplotypes on patients' responses to particular warfarin doses [*N Engl J Med* 2005; **352:** 2285].

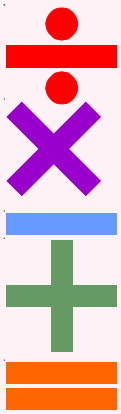
Looking at *VKORC1* haplotype frequencies in African-American, European-American, and Asian-American populations as well as VKORC1 messenger RNA (**mRNA**) levels in human liver samples, Mark Rieder and coworkers identified 10 common noncoding *VKORC1* SNPs and inferred five major *haplotypes* (pattern of DNA variant sites along one chromosome, across one gene). A low-dose haplotype group (***A***) and a high-dose haplotype group (***B***) were identified. The average maintenance dose of warfarin differed significantly among the three haplotype group combinations**:** 2.7 ± 0.2 mg per day for ***A/A***, 4.9 ± 0.2 mg per day for ***A/B***, and 6.2 ± 0.3 mg per day for ***B/B*** patients (*p* value <0.001).

It was calculated that these *VKORC1* haplotype groups A and B can account for ~25% of the variance in warfarin dosages seen in clinical populations. Asian-Americans had a higher proportion of group A haplotypes, and African-Americans a higher proportion of group B haplotypes. VKORC1 mRNA levels paralleled the haplotype combinations, suggesting the genetic difference occurs at the level of gene transcription.

This polymorphism is one of several dozen "high-penetrance, predominantly monogenic" traits that might help the clinical pharmacologist in deciding upon how to dose individual patients with particular drugs [*Eur J Pharmacol* 2004; 500: 267]. The downside, however, is for the physician (or patient) to put too much emphasis on the DNA test. For example, in this current study, the contribution of this polymorphism to an individual patient's warfarin response is 25%, meaning there's another 75% that remains unknown.

A simple formula for success

Begin with a dream



the problems

the possibilities

the negative

enthusiasm

success

Quitting smoking is easy, I've done it thousands of times.

FOR ALL YOU LEXOPHILES

A bicycle can't stand alone because it is **two-tired.**

What's the definition of a will? (**It's a dead giveaway.**)

A backward poet writes **inverse.**

In a democracy, it's your vote that counts; In feudalism, it's your count that votes.

A chicken crossing the road is **poultry in motion.**

If you don't pay your exorcist, you get **repossessed.**

When a clock is hungry, it "goes back **four seconds**".

The man who fell into an upholstery machine is fully **recovered.**

A grenade thrown into a kitchen in France would result in **Linoleum Blownapart.**

You feel stuck with your debt if you can't **budge it.**

Local Area Network in Australia: the **LAN down under.**

He had a photographic memory that was never **developed.**

A plateau is the highest form of **flattery.**

A short fortuneteller who escaped from prison is **a small medium at large.**

When you've seen one shopping center you've seen **a mall.**

Those who jump off a Paris bridge are **in Seine.**

Bakers trade bread recipes on a **knead-to-know basis.**

Acupuncture is a **jab well done.**

Marathon runners with bad footwear suffer the **agony of "de-feat".**

Van Gogh's Family Tree

His dizzy aunt.....Verti Gogh

The uncle at a convenience store.....Stop n Gogh

The grandfather from Yugoslavia.....U Gogh

The cousin from Illinois.....Chicahh Gogh

His magician uncle.....Where-diddy Gogh

His Mexican cousin.....A mee Gogh

A son driving an armored car.....Wells-far Gogh

The ballroom dancing aunt.....Tang Gogh

The bird lover uncle.....Flamin Gogh

His nephew psychoanalyst.....E Gogh

The fruit loving cousin.....Man Gogh

The positive thinking aunt.....Way-to Gogh

The little bouncy nephew.....Poe Gogh

A sister who loved disco.....Go Gogh

A son with a van.....Winnie Bay Gogh

And there ya Gogh!.....

Newton said, "I do not know what I may appear to the world, but to myself I seem to have been only like a boy playing on the seashore...whilst the great ocean of truth lay all undiscovered before me."

NEW CEG Director

Alvaro Puga, PhD

Alvaro took the director-ship in the summer of 2005. We welcome his leadership and expertise, and wish him well in this endeavor

CEG Members in the News

Dan Nebert was the Plenary Speaker at the 35th Annual Meeting of the European Environmental Mutagenesis Society, held on the Island of Kos, Greece (Jul 2005) and also an Invited Speaker at the 12th Annual Mount Desert Island Biological Laboratory Environmental Health Sciences Symposium on "Molecular evolution of chemical defense mechanisms," at Bar Harbor, Maine (Jul 2005). He also was selected as one of ten lecturers to talk to ~500 incoming University Cincinnati Honors Freshmen in their class**:** "Five Pillars of Honor**:** Leadership, Global Studies, Community Engagement, Research & Creative Arts, and Interdisciplinary

Nancy Steinberg-Warren, is developing an online teaching course "Teaching genetics online**:** Information for undergraduate communication disorders students." As well as being coauthor on several posters sessions, **Nancy** also presented a talk at the National Society of Genetic Counselors Annual Education Meeting, Los Angeles, CA (Nov 2005).

Welcome!

The Deptartment of Environmental Health is pleased to announce the arrival of its new Chair, **Shuk-mei Ho, PhD**, from University of Massachusetts Medical School. Her research field has been the study of the significance of hormones and endocrine disruptors on tumorigenesis in the prostate, ovary, endometrium and breast. She utilizes genomic, epigenomic, proteomic, and bioinformatic analyses for the discovery of diagnostic and prognostic cancer markers and for the prediction of patients' responses to interventions. Her current program emphasizes mechanisms of fetal-based adult disease development, cadmium-induced disorders, and oxidative stress/inflammation-mediated cellular changes. She arrived on Sep 1, 2005.

She was accompanied by Drs. Ying-wai Lam, Neville Tam, Ricky Leung, Xiang Zhang, Winnie Tang and Sonia Godoy Tundidor.

Dr. Lam's expertise is in biomarker discovery and monitoring using state-of-the-art proteomic technology. Dr. Tam's research interest is to understand the early events of prostatic carcinogenesis, with emphasis on the role of oxidative/nitrosative stress and the related tissue injuries. Dr. Leung's research focuses on the impact of natural and xeno-/environmental estrogens on hormone-dependent tissues. Dr. Zhang studies the genetic and epigenetic change of proto-oncogene and tumor suppressor genes during carcinogenesis. Dr. Tang's major research interest is the epigenetics of fetal-based adult disease development after exposure to environmental disrupting chemicals. Dr. Godoy Tundidor's research specializes in unraveling the consequences of androgen-withdrawal therapies in the reawakening genes that had been initially repressed by the androgen receptor signaling axis.

Supreme Court rules punishment of criminals violates their civil rights.

SCIENCE LITE

Those Grand Old Burma Shave Road Signs

Remember these? For those who never saw any of the Burma Shave signs, here is a quick lesson in our history of the 1930s -1950s. Before there were interstates, when everyone drove the old 2-lane roads, or rode the trains, Burma Shave signs would be posted all over the countryside in farmers' fields. They were small red signs with white letters. Five signs, about 100 feet apart, each containing one line of a 4-line couplet.....and the obligatory 5th sign advertising Burma Shave, a popular shaving cream. Here are some of the actual lyrics:

TRAINS DON'T WANDER
ALL OVER THE MAP
'CAUSE NOBODY SITS
IN THE ENGINEER'S LAP
Burma Shave

SHE KISSED THE HAIR-BRUSH
BY MISTAKE
SHE THOUGHT IT WAS
HER HUSBAND JAKE
Burma Shave

HE LIT A MATCH
TO CHECK HIS TANK
THAT'S WHY THEY CALL HIM
SKINLESS FRANK
Burma Shave

DON'T LOSE YOUR HEAD
TO GAIN A MINUTE
YOU NEED YOUR HEAD
YOUR BRAINS ARE IN IT
Burma Shave

DROVE TOO LONG
DRIVER SNOOZING
WHAT HAPPENED
NEXT IS NOT AMUSING
Burma Shave

BROTHER SPEEDER
LET'S REHEARSE
ALL TOGETHER
GOOD MORNING, NURSE
Burma Shave

CAUTIOUS RIDER
TO HER RECKLESS DEAR
LET'S HAVE LESS BULL
AND MORE STEER
Burma Shave

SPEED WAS HIGH
WEATHER WAS NOT
TIRES WERE THIN
X MARKS THE SPOT
Burma Shave

THE MIDNIGHT RIDE
OF PAUL FOR BEER
LED TO A WARMER
HEMISPHERE
Burma Shave

AROUND THE CURVE
LICKETY-SPLIT
BEAUTIFUL CAR, …
WASN'T IT?
Burma Shave

NO MATTER THE PRICE
NO MATTER HOW NEW
THE BEST SAFETY DEVICE
IN THE CAR IS YOU
Burma Shave

A GUY WHO DRIVES
A CAR WIDE OPEN
IS NOT THINKIN'
HE'S JUST HOPIN'
Burma Shave

AT INTERSECTIONS
LOOK EACH WAY
A HARP SOUNDS NICE
BUT IT'S HARD TO PLAY
Burma Shave

BOTH HANDS ON THE WHEEL
EYES ON THE ROAD
THAT'S THE SKILLFUL
DRIVER'S CODE
Burma Shave

A CHIN WHERE
BARBED WIRE BRISTLES STAND
IS BOUND TO BE
NO MA'AMS LAND
Burma Shave

THE ONE WHO DRIVES
WHEN HE'S BEEN DRINKING
DEPENDS ON YOU
TO DO HIS THINKING
Burma Shave

CAR IN DITCH
DRIVER IN TREE
THE MOON WAS FULL
AND SO WAS HE.
Burma Shave

MY JOB IS
KEEPING FACES CLEAN
AND NOBOTY KNOWS
DE STUBBLE I'VE SEEN
Burma Shave

SOAP MAY DO
FOR LADS WTIH FUZZ
BUT SIR, YOU AIN'T
THE KID YOU WUZ
Burma Shave

I KNOW HE'S A WOLF
SAID RIDING HOOD
BUT GRANDMA DEAR
HE SMELLS SO GOOD
Burma Shave

PASSING SCHOOL ZONE
TAKE IT SLOW
LET OUR LITTLE
SHAVERS GROW
Burma Shave

What's especially nice to see is the environmentally and socially conscious statements that were made: integrity is endangered.

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I Genes and the Environment
Center for Environmental Genetics
University of Cincinnati
Cincinnati, Ohio 45267-0056
Fax: 513-558-0925 and 513-821-4664
E-mail: dan.nebert@uc.edu

Subscribe to
CEG-*INTERFACE*
at listserv@listserv.uc.edu

next-Best Typo
"Benomics"

- **If you are irreplacible, you can't be promoted.**
- **Remember that you're unique, but so is everyone else.**
- **Never test the depth of the water with both feet.**
- **Of course somebody cares about you, your creditors.**
- **Before you criticize someone, you should walk a mile in their shoes; that way, when you do criticize, you have their shoes and a mile headstart.**
- **Give a man a fish and he will eat for a day. Teach a man to fish, and he will sit in a boat and drink beer all day--- or ----Give a man a fish and he will eat for a day. Teach a man to use the internet, and he will need to be fed forever.**
- **If you lend someone $20 and never see that person again, it was probably worth it.**
- **Everyone seems normal until you get to know them.**