



INTERFACE:

GENES AND THE ENVIRONMENT

CENTER FOR ENVIRONMENTAL GENETICS UNIVERSITY OF CINCINNATI SUMMER/FALL 2003

Marshall W Anderson, PhD, Director

Daniel W Nebert, MD, Editor

Marian L Miller, PhD, Assistant Editor

Cigarette Smoking: The Good(?), The Bad, and The Ugly

We know that cigarette smoking is unhealthy, we teach this message to our children, and children learn this in school and tell their parents. Smoking cigarettes is associated with an increased risk of developing many different diseases, but did you know that smoking is sometimes associated with a *decreased* risk of certain maladies? Whereas we would never advocate cigarette smoking to anyone, this article provides an overview of what is **Good(?)**, what is **Bad**, and what is **Ugly** about smoking cigarettes. We will start this brief review with the last item (**Ugly**) and move forward.

Smoking Is Ugly

Cigarette smoking is the single largest preventable cause of premature death and disability in the U.S. One in every five deaths in the U.S. is smoking-related. Every year, smoking kills more than 276,000 men and 142,000 women prematurely from diseases such as cancer (many types), emphysema, stroke, and heart attack. In 2000, an estimated 8.6 million persons in the U.S. had an estimated 12.7

million smoking-attributable conditions—including chronic bronchitis (49%), emphysema (24%), and previous heart attack (24%). Lung cancer accounted for 1% of all cigarette smoking-induced illnesses. These findings [1] indicate that more persons are harmed by tobacco use (health problems, *i.e.* **morbidity**) than is indicated by mortality estimates. Moreover, it is likely that these self-reported data are substantial underestimates of the true disease burden.

Approximately 10% of all current and former adult smokers have a smoking-attributable chronic disease. Men who smoke increase their risk of death from lung cancer by more than 22 times and from bronchitis and emphysema by nearly 10 times. Women who smoke increase their risk of dying from lung cancer by nearly 12 times and the risk of dying from bronchitis and emphysema by more than 10 times. Smoking triples the risk of dying from heart disease among middle-aged men and women.

Lung cancer. About 10% of long-term smokers will eventually be diagnosed with lung cancer [2]. Among the 10% of patients who develop lung cancer without a smoking history, the environmental versus the inherited causes of lung cancer are usually unclear. There is no validated screening method for lung cancer, even in high-risk populations, and the overall 5-year survival rate has not changed significantly in the last 20 years. For the past five decades, lung cancer has been the **Number One** cause of cancer mortality in American men; in 1986, lung cancer surpassed breast cancer as the leading cancer of American women. Because cancer generally takes 25–40 years to become manifest, this increase in lung cancer among women undoubtedly reflects the large increase in women smoking cigarettes since the 1940s.

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Other cancers that occur much more frequently in smokers than in nonsmokers include: head-and-neck squamous cell carcinoma (HNSCC; mouth, throat, larynx), and cancer of the urinary bladder, esophagus, colon, and rectum. Several epidemiological studies have shown a correlation between cancer risk (of the bladder and colon, for example) and certain genotypes (high CYP1A2 and *N*-acetyltransferase NAT2 activity; deletion of either or both of the *GSTM1* and *GSTT1* genes) [3–6]. There appears to be a slightly increased risk among cigarette smokers for cancer of the uterine cervix, kidney, pancreas, sinuses, breast, thyroid, lymphatic system (*e.g.* lymphoma), and blood (*e.g.* leukemia).

Emphysema. Emphysema is a long-term, progressive disease of the lung that primarily causes shortness of breath. In people with emphysema, the lung tissues necessary to support the physical shape and function of the lung are destroyed. Destruction of lung tissue around smaller airways, called bronchioles, makes these airways unable to hold their shape properly when you exhale. Emphysema is included in a group of diseases called chronic obstructive pulmonary disease (COPD). This COPD group of diseases ranks as the fourth leading cause of death in the United States. Unlike heart disease and other more common causes of death, the death rate for COPD appears to be rising. Smoking accounts for more than 85% of emphysema mortality in America.

Stroke and peripheral arterial occlusive disease (PAOD). Smoking is a major risk factor for stroke (loss of normal blood supply to the brain), as well as PAOD (the narrowing of blood vessels that carry blood to the leg and arm muscles). If a blood clot blocks an already narrowed artery, then the result could be the damage to, or even loss of, an arm or leg.

Coronary heart disease. Smoking is a major risk factor for heart attacks. Also, smokers who have a heart attack are less likely to survive than a person who does not smoke. And by continuing to smoke after a heart attack, the person's chance for a second attack increases.

Environmental tobacco smoke (ETS). Exposure to secondhand smoke (which can be exposure to combustion of fossil fuels, wood stoves, campfires, and diesel exhaust, etc., as well as cigarette/cigar/pipe smoking) causes an estimated

3,000 deaths from lung cancer each year in the U.S. Studies also link secondhand smoke to heart disease.

Smoking Is Bad

Economy. Smoking has severe economic consequences for the U.S., estimated at a staggering \$53.7 billion in total annual costs. Direct costs account for \$30.4 billion of the total; there is an additional annual cost of \$23.3 billion in lost productivity due to excess morbidity and mortality. Each year in the U.S., smoking-attributable illnesses result in 5.6 million years of potential life lost, \$75 billion in direct medical costs, and \$82 billion in lost productivity.

Lowered birth weight. Children born of cigarette-smoking mothers are smaller in weight at birth. For each cigarette smoked per day, the newborn is (on average) 9 grams lighter. For pack-a-day smokers, this means 180 grams (6 ounces) lower birth weight. Smoking by the mother also causes an increased risk to the baby for a variety of congenital diseases and birth defects.



Asthma and children's health. Exposure to ETS contributes to health problems in children and is a significant risk factor for asthma. Also, cigarette smoke contains chemicals that appear to lower a person's defense systems leading to more viral colds and other respiratory infections.

Nicotine addiction. Nicotine addiction, almost always the result of smoking cigarettes, is the most widespread example of drug dependence in our country. Nicotine dependence often begins with the first few cigarettes smoked during adolescence. Teen tobacco use is fueled by the attractive social images that tobacco companies create for their products.

Three-quarters of the adults who currently smoke started their habit before age 21; teenage years are critical for developing cigarette smoking addiction [7]. Although many people smoke because they believe cigarettes calm their nerves, smoking actually releases epinephrine—a hormone that causes physiological stress in the smoker, rather than relaxation. Most users develop tolerance for nicotine and need greater amounts to produce the same desired effect. Smokers become physically and psychologically dependent and will suffer withdrawal symptoms including: changes in body temperature, heart rate, digestion, muscle tone, and appetite; irritability, fatigue, nausea, anxiety, sleep disturbances, nervousness, headaches, and cravings for tobacco that can last weeks, months, or an entire lifetime.

Increased wrinkling. By age 40-50, the facial wrinkles of smokers are similar to those of nonsmokers 20 years older. Part of this effect might be the nutritional depletions from smoking and direct effects on collagen fibers under the skin. Extra emphasis to young people might be made about smoking-associated facial wrinkling, as a possible deterrent to discourage long-term smoking.

Smoker's face. Unique to smokers, this condition is a combination of wrinkles, gaunt features, sagging skin, and an oddly-colored complexion. One study showed excessive wrinkling even among 40- and 50-year-olds who only smoked during their teens and twenties. Smokers who quit can regain their pink cheeks, but they will never lose their wrinkles. Wrinkles and smoker's face are more pronounced in Caucasian than in Black or Asian smokers.

Additional problems. Additional risks associated with smoking cigarettes include: chronic bronchitis (smoker's cough and increased phlegm), stomach ulcers, increased heart rate and blood pressure, greater risk of osteoporosis (thinning of bone), frequent colds, diminished or extinguished sense of smell and taste, and an increased risk, or flare-up of, Crohn's disease (an inflammatory or autoimmune disorder of the small intestine) as well as rheumatoid arthritis [8]. Cigarette smokers also experience a higher risk for cataracts, gum disease, tooth decay, ear infections, dry skin, impotence, slower rate of wound healing, and decreased circulation in the fingers and toes. Smokers are more prone to premature thinning and graying of the hair. Men who smoke are twice as likely to become bald as men who do not smoke; premature graying is three to six times more common in smokers. Because it takes a longer time for smokers to heal and there is more

scarring, cigarette smokers are advised to stop smoking immediately before and after plastic surgery.

Smokeless tobacco. Snuff in the U.S. is sniffed through the nose, whereas chewing tobacco is placed in the mouth and/or chewed rather than smoked, meaning there is little exposure to the types of harmful chemicals present in cigarette smoke, although both can deliver high doses of nicotine [9]. Both can be habit-forming, but snuff does not appear to cause cancer or respiratory disease. Chewing tobacco, on the other hand, is associated with cancer of the oral cavity. Both may cause a slight increase in cardiovascular risks and are likely to be harmful to the developing fetus, although these risks are lower than those caused by smoking.

Can Smoking Sometimes Be Good?

Loosening sputum. Many physicians treating patients with COPD or other serious smoking-induced diseases find that they continue to smoke, despite the obvious fact smoking makes their cough worse. The invariable answer as to why they continue to smoke, if smoking makes their cough worse, is that the cigarette-induced cough loosens their sputum; this seems to be a universal response of cigarette smokers.

Ulcerative colitis. Smoking cigarettes is associated with a decreased risk for ulcerative colitis (ulcers in the large intestine that are so severe that the colon is usually removed before age 25). It has been assumed that nicotine is the active agent in these associations; however, clinical trials of nicotine chewing gum and trans-dermal nicotine in ulcerative colitis patients have shown limited benefit, and have been complicated by significant side-effects [8].

Parkinson disease (PD). This disease is caused by some defect in the substantia nigra, an area within the central nervous system (CNS). When PD occurs before age 50, such as occurred with the movie star Michael J. Fox, the disorder is strongly associated with a genetic predisposition. After age 50, which happens with PD more than 99% of the time, there is little or no genetic predisposition and the disorder is believed to be caused predominantly by the environment [10]. Whether environmental chemicals cause oxidative stress and abnormal protein handling, or vice versa, is not yet known. A limited number of environmental chemicals (*e.g.* pesticides such as rotenone) are known to be toxic to the substantia nigra; in contrast, some factors such as caffeine intake and cigarette

smoking appear to protect against the development of PD [11]. The mechanisms are not known.

Schizophrenia. Close to 100% of all schizophrenic patients smoke cigarettes because they say “It makes them feel better.” The secretion of neurotransmitters—such as noradrenaline, serotonin, dopamine, acetylcholine, 8-amino-butyric acid (GABA), and glutamate—is increased by the binding of nicotine to CNS nicotine receptors. Some studies suggest that serotonin formation and secretion in patients with mental illness are influenced by chronic smoking. Cigarette smoke inhibits the activity of monoamine oxidase B, which is responsible for the degradation of several brain neurotransmitters. In patients with schizophrenia treated with neuroleptics, cigarette smoking reduces adverse reactions to the drug therapy, presumably because of an increase in metabolism of the neuroleptics [12]. Still, we do not really understand why smoking helps schizophrenic patients.

Uterine fibroids. Uterine leiomyomata are hormonally-dependent tumors that are a major source of gynecologic problems among women of reproductive age. Relatively few studies have attempted to identify specific risk factors for these neoplasms, but the incidence of uterine fibroids is considerably less among cigarette smokers.

Endometriosis. Endometriosis was discussed in an earlier issue of *Interface*, because dioxin is known to increase endometriosis in monkeys. Often in the form of “chocolate cysts” of the ovary, endometriosis commonly occurs in sisters and has been reported in mother and daughter(s). Endometriosis is a common gynecologic disorder that accounts for infertility in more than 10% of women of reproductive age; however, relatively little is known about what causes the disease. Several studies have suggested that endometriosis has a multifactorial etiology including hereditary, hormonal, and immunologic factors. The incidence of endometriosis is known to be less in cigarette smokers.

The incidence of vomiting during pregnancy and of benign breast disease is also decreased in cigarette smokers. The control of weight gain and appetite is also benefited by smoking cigarettes.

Aphthous ulcers. Behcet syndrome includes recurrent inflammatory lesions of the mouth, genitalia, eyes, and sometimes arteries; viral and autoimmune causes have been suggested. In a Behcet syndrome patient’s family, there are sometimes multiple members with other autoimmune diseases. Some of

the symptoms in patients with Behcet syndrome can be activated after the patient has stopped smoking [13].

Using this knowledge to understand the cause of disease

Obviously, with all the ugly and bad diseases described above, cigarette smoking cannot be recommended to any patient. We should consider seriously, however, the possibility that we might understand more about the mechanism (cause, etiology) of each of these diseases listed in this section, if we could delineate the reasons why cigarette smoking helps the disorder. Numerous mechanisms for the beneficial effects of smoking have been proposed, but the three major theories include: (a) the “anti-estrogenic effect” of cigarette smoke; (b) alterations in prostaglandin production; and (c) stimulation of nicotinic cholinergic receptors in the CNS [14]. The reactive polycyclic aromatic hydrocarbons (PAHs) in cigarette smoke are known to exert anti-estrogenic effects by way of the aryl hydrocarbon receptor (AHR; discussed in earlier issues of *Interface*) and to stimulate prostaglandin pathways (PAHs induce cyclooxygenase-2 as one of the first steps in prostaglandin production). PAHs also cause oxidative stress and stimulate oxidative-stress-related signal transduction pathways and stress response pathways. Although nicotine’s interference, or stimulation, of nicotinic receptors in the CNS may help decrease the symptoms of schizophrenia, it is of interest that differences in the gene encoding a cigarette smoke-inducible aldehyde dehydrogenase (*ALDH3A1*) have recently been associated with schizophrenia [15]. -----Contributed by Dan Nebert

References

1. *Morbidity & Mortality Weekly Report* 5 Sept 03; **52**: 842–844.
2. *Cancer Biol Ther* 2004; **3**: [Epub ahead of print].
3. *Int J Cancer* 1994; **59**: 728–738.
4. *Carcinogenesis* 1998; **19**: 37–41.
5. *IARC Sci Publ* 1999; **148**: 173–195.
6. *Cancer Epidemiol Biomarkers Prev* 2003; **12**: 882–889.
7. *Semin Oncol Nurs* 2003; **19**: 261–267.
8. *Eur J Gastroenterol Hepatol* 2000; **12**: 855–862.
9. *Tob Control* 2003; **12**: 349–359.
10. *J Am Med Assn* 1999; **281**: 341–346.
11. *Can J Neurol Sci* 2003; **30**(Suppl 1): S10–S18.
12. *Int J Clin Pharmacol Ther* 2002; **40**: 404–418.
13. *Clin Rheumatol* 2000; **19**: 508–509.
14. *Br Med Bull* 1996; **52**: 58–73.
15. *Mol Psychiatry* 2004; **9**: [Epub ahead of print].

LETTERS TO THE EDITOR

RESPONSES/COMMENTS TO VARIOUS QUESTIONS

COMMENT In the last issue of *Interface*, we had predicted that it would not be long before the first race horse is cloned. Well, the first mule has been cloned [*Science* 2003; 301: 1063]. A few months later, these same scientists (at University of Idaho and Utah State University, Logan) also reported a second and third mule successfully cloned. Now, the first horses have been cloned, in a report from Italy [*Nature* 2003; 424: 635] and another report from Colorado [*Nat Genet* 2003; 34: 363]. So, we have had sheep, mice, cows, goats, rabbits, cats, pigs, mules, and now horses—successfully cloned. No monkeys or humans yet (contrary to sensationalistic newspaper articles saying otherwise); something seems to be technologically more difficult in primate (monkey, human) embryonic cells that we do not yet understand.

Q Your last issue described the transgenic fish being used to detect pollutants in drinking water by introducing “fluorescent” reporter genes. In the newspaper, I see someone else in Southeast Asia has also developed such fish?

A Yes, the leading article in our last issue of *Interface* described the development of transgenic zebrafish to use as sentinels for detecting aquatic pollution. Such a transgenic fish for home aquariums (*GloFish™*) has now been developed (by Zhiyuan Gong, National University of Singapore), but there may be problems in the form of federal regulations against selling such fish “for fear of releasing foreign genes into wild fish populations” [*Nature* 2003; 426: 372]. In fact, California has now passed a law forbidding the sale of these glowing fish to people wanting them for their home aquariums [*Nature* 2003; 426: 596].

Q Two scientists won the Nobel Prize for Physiology and Medicine for their work on magnetic resonance imaging (MRI), but I heard something on National Public Radio that the Prize seems to have been given to the wrong scientists. What’s the story?

A You are correct in that physicists Paul Lauterbur and Peter Mansfield were awarded the Nobel Prize in Sweden for their work on MRI. Quite a number of colleagues in the field strongly objected that Raymond Damadian (New York), and perhaps Vladislav Ivanov (St. Petersburg, Russia) were more accurately the true founders of the principles of MRI technology. In fact, a Swedish group (*Idéforum*) came to New York and gave Dr. Damadian an alternative award on the same day the Nobel Prize was being awarded to Drs. Lauterbur and Mansfield in Stockholm [*Nature* 2003; 426: 375, 596].

COMMENT Thank you for issue 25 of *Interface*. It is an excellent newsletter. It is interesting, informative, succinct, with a light hearted and user friendly style. The numerous citations are greatly appreciated. Great Job. Keep up the good work.

Q Dear Sir, I hope that this email finds you well. I wanted to ask (and perhaps inform) you whether you knew you were a Googlewhack? A Googlewhack if you are not aware is a single site that is found by entering two words into the Google search engine. The words must appear in "www.dictionary.com" and cannot be a list of words. I used "pharmacogenetics" and "anteater" and up popped the following site: "www.eh.uc.edu/ceg/wwinte21.pdf" As you are the editor, I thought you may be interested in this rather unusual fact. Because Google has catalogued over 3

billion web pages, it is practically impossible to find a single "hit" when entering two words only. That's why we enter completely ridiculous, unconnected words, like pharmacogenetics and anteater! Now, why two completely unrelated words would then generate a single site is beyond me!!

A Thank you for that information. No-offense, but perhaps Googlewhack searchers could be labelled Googlewhackwackos.

OO Nice - I like it! And no offense taken. Having said all this, I bet you are now trying to find one. Go on - admit it!! (Sure, I don't mind if you state you are a Googlewhack. Might be fun seeing that term in the context of the serious scientific data in a newsletter!)

AA Yes, we have tried, unsuccessfully, to find another Googlewhack (LOL).

Additional Complexity to the Genome!

We now have the sequence of the human and mouse and other genomes, and it's sort of like finding out all the letters, arranged in order, in a large book. But when will we learn how to read the book and understand it? Many labs are trying to identify all the putatively functional genes, and so far this gene-counting problem has not been completely solved [*Science* 2003; **301**: 1040]. One method is to compare genomes from similar organisms (two yeasts, two nematodes, two insects, two sea squirts, two plants, two mammals).

Intriguingly, the problem grows more complex, because there have recently been discovered thousands of non-expressed **conserved sequence elements** (CSEs) when the mouse and human genomes were compared [*Genome Biol* 2003; **4**: R1], sequences having a median length of ~500 bases whose function we do not understand. Some are possibly promoter regions, some are pseudogenes or RNA genes, and some are new undocumented genes, but it is clear that this does not account for all of these sequences. Another approach was to analyze DNA sequence from 12 species, all derived from a 1.8-Mb region orthologous to a human Chr 7 segment containing 10 genes [*Nature* 2003; **424**: 788]. In this instance, coding exons were already well documented, but substantial numbers of CSEs—beyond those previously identified experimentally—were discovered.

Whereas ~1.5% of the human genome comprises protein-coding genes, another ~3.5% of the genome contains CSEs that are more conserved than protein-coding-gene regions [*Science* 2003; **302**: 1033]. Possible functions for these CSEs (termed CNGs by Dermitzakis et al. [*Science* 2003; **301**: 1176] and CNSs by Inada et al. [*Genome Res* 2003; **13**: 2030]) include control regions that: [a] regulate gene expression; [b] govern developmental-, cell type- and organ-specific expression, in *trans*, of genes located far away; [c] lock-in regulatory decisions; and [d] act as structural components of chromosomes when alignment and chromosome movement occurs during meiosis or mitosis. **There appear to be at least twice as many CSEs than protein-coding genes in the genome;** so, if the human gene count makes it to 40,000, this means we have more than 80,000 CSEs to deal with. A recent comparison of 43 species—including vertebrates, insects, worms, plants, fungi, yeast, eubacteria and archaeobacteria [*Science* 2003; **302**: 1401]—revealed noteworthy increases in genome size and complexity from prokaryote to mammals, again emphasizing the innumerable highly-conserved CSEs are likely to have essential functions and critical effects on an organism's phenotype.

The bottom line is that we are not even close to unravelling the mysteries of the genome, let alone identifying with certainty the precise number of functional genes.

Biotechnology, ...

Tidbits concerning genetically-modified (GM) plants, biotechnology, and related topics:

Jul 2003 Nearly one-fifth of farmers in the U.S. are ignoring federal rules and guidelines about how much *transgenic corn* they can plant. Experts fear that this non-compliance could encourage insects to develop resistance to the insecticide produced by the crop [*Nature* 2003; **424**: 116].

Consumer surveys in Europe suggest that shoppers there won't buy food that is labeled as "containing transgenic (or GM) material," and several leading supermarket chains have refused to stock such material and are expected to continue doing so [*Nature* 2003; **424**: 116].

Aug 2003 In past issues of *Interface*, we have described the problems of deformed frogs plaguing various parts of the world, especially around the Great Lakes, with no obvious etiology. Now comes a report that *parasites* could explain these malformations [*Science* 2003; **301**: 904], and that nutrient runoff from cow pastures and farmers' fields might be stimulating populations of snails, which host the parasite (a trematode called *Ribeiroisia*).

Studying a toxic waste dump site of *used batteries* in a cove on the Hudson River in New York that has ~53 tons of cadmium and nickel, researchers found that the oligochaete *Limnodrilus hoffmeisteri* (a terrestrial and aquatic worm having bristles singly on each segment along the entire length of its body) developed resistance to these heavy metals; removing the worm from this dump site resulted in a rapid loss of resistance after 9-18 generations [*PNAS* 2003; **100**: 9889].

Cloning a wheat gene into mutant *Arabidopsis thaliana* (tiny mustard) plants resulted in transgenic plants that can remove heavy metals (arsenic, mercury, cadmium) from soil, a form of phytoremediation [*PNAS* 2003; **100**: 10118].

Sep 2003 Britain and other European Union countries will begin voting later on whether to license some 15 new varieties of transgenic crops, ending a 5-year moratorium. The trouble is, environmentalists are very active in trying to convince the public not to buy such GM foods [*Nature* 2003; **425**: 331].

Oct 2003 The pig's genome has begun to be mapped. A study from Sweden found that the insulin-

like growth factor-2 gene (*IGF2*) had a single mutation in some pigs, which added 3-4% more meat to a pig [*Nature* 2003; **425**: 777, 832]. This pig—with more muscle and less fat—will be a boon for the consumer.

Nov 2003 Crops growing in untilled soil take advantage of resident microorganisms such as mycorrhizal fungi, but this plant-fungi interaction also requires "helper" bacteria. In a clever set of experiments, Swedish scientists determined that a particular strain of *Bacillus cereus*, which has a polar flagellum, is the helper [*Appl Environ Microbiol* 2003; **69**: 6208].

Dec 2003 The Human Epigenome Project (HEP), a 5-year undertaking to map all DNA-methylation sites throughout the human genome, has been launched by the Wellcome Trust Sanger Institute (England) and Epigenomics AG (Berlin) [*PLoS Biol* Dec 2003; **issue 3**]. **Epigenetics** includes "regulatory effects on inheritance and gene expression that are not controlled in the classical means by Mendelian genetics (e.g. DNA methylation, RNA silencing, histone acetylation, imprinting)."

French-fry and pizza cartons contain fluorinated telomers, a polymer to keep grease from seeping through paper and cardboard packaging. Studies by the 3M company in 2001 found perfluorooctanoic acid (**PFOA**) detectable in the blood of 96% of children tested in 23 States [*Environ Health Perspect* 2003; **111**: A872].

Korea announced the birth of four transgenic calves that are resistant to mad-cow disease (bovine spongiform encephalopathy, **BSE**). This shows great promise. Maybe, before too many years, we'll have cows world-wide that are "BSE-proof" [*Nature* 2003; **426**: 743].

Several past issues of *Interface* have discussed "knock-down" experiments in which gene expression at the mRNA level is ablated by RNA interference (RNAi). Now there is a general method for **protein knock-down** [*PNAS* 2003; **100**: 14127]...!!

The Massachusetts Institute of Technology (MIT), Harvard, and Weizmann Institute of Science (Rehovot, Israel) have all begun departments of **Systems Biology** this year, to focus on quantitative biology and complex signal transduction circuitry inside the cell and within an organism [*Science* 2003; **302** 1646].

When studying mRNA (cDNA) expression on DNA microarray chips, the problem of RNA degradation is now being addressed, in order to enhance reproducibility of the experiments [*Nat Genet* 2003; **35**: 292].

The National Human Genome Research Institute (NHGRI, Bethesda) has selected **five centers** to carry out a new generation of large-scale sequencing projects: Agencourt Bioscience Corp. (Beverly MA), Baylor College of Medicine (Houston TX), The Eli &

Edythe L. Broad Institute (MIT, Cambridge MA), The Institute for Genomic Research (Rockville MD), and Washington University School of Medicine (St. Louis MO).

Our most endangered resource is----possibility thinking!

Observations by a Biologist

How Can We Best Study Human Complex Diseases in Lab Animals?

Human complex diseases include arthritis, asthma, cancer, diabetes, heart disease, obesity, osteoporosis, stroke, alcoholism, addiction, and drug or environmental chemical toxicity. Geneticists trying to sort out the genes that cause some of these most common human complex diseases need to capture the natural variation that exists in human populations that can be studied reproducibly in a lab animal model system. The Human HapMap and Mouse HapMap projects have been proposed and are underway, but they seem plagued with problems and it is doubtful to many of us how valuable this HapMap information will be (discussed in earlier issues of *Interface*). On the other hand, the 2nd Annual Meeting of the Complex Trait Consortium (in Oxford, England, 1–3 Jul 2003) led to an exciting proposal to create as many as 1,000 new lines of mice—in a novel approach to studying human complex diseases.

Recombinant inbred (RI) mouse lines have been around since before 1970. Basically, one makes an RI line by crossing inbred strain A with inbred strain B, crossing the AB F₁ offspring to produce F₂ offspring, and then making brother-sister crosses for at least eight generations. This procedure, which might result in 30 or more lines each arising from the original F₂ brother-sister mating, *fixes* the two alleles at each gene (locus) as either AA, AB or BB. Each RI line then serves as “a

unique individual,” no matter how many mice you may study from that line.

The geneticists, statisticians, and other biologists developed a scheme to cross the eight most diverse inbred strains for four generations, producing litters with all 1,680 possible permutations of great-grandparents. This will be followed by brother-sister matings for 20 generations to produce about 1,000 RI lines, which will take about 7 years. These lines will then become invaluable for tracking down regions of the genome that seem to play a role in complex diseases (quantitative trait loci) (QTLs) (*e.g.* does this region contribute 5% or 23% to the trait? etc.). One of the factors confounding human research is that people who carry a susceptible gene may also carry other protective genes—thereby masking the effect of the disease-prone allele in epidemiological studies.

This approach [*Science* 2003; **301**:456] seems to be an extremely systematic, promising way to focus on human complex diseases in a lab animal model system. On a very much smaller scale, this basic approach was carried out in the early 1970s by Gerald McClearn at the University of Colorado (Boulder), who developed RI lines that are exquisitely sensitive or resistant to ethanol in order to study various parameters of alcoholism.

 **Quote of the month** An idea that isn't risky is hardly worth calling an idea.....Oscar Wilde, Oct 16, 1854 - Nov 30 1900

Blessed are the flexible, for they shall not be bent out of shape.

web-cytes

To understand chemical reactions, on a web site that includes everything from animated flights across the surface of a protein to a video of various substances going up in flames to explain chemical reactions, check out <http://neon.chem.ox.ac.uk/vrchemistry>. To carry out more than 20 laboratory chemistry experiments in a *virtual lab*, check out ir.chem.cmu.edu/irproject/applets/virtuallab. Another site shows 100 short animations for beginning chemistry and biochemistry students ull.chemistry.uakron.edu/genobc/animations/index.html. And a similar site for physics students www.physicsweb.org. And a similar site for undergraduate biology students, complete with preliminary quizzes www.biology.arizona.edu.

Students who need a refresher course on *more advanced* chemical reactions (electronegativity, electron properties in a chemical bond, “boat” versus “chair” conformation, etc.) might want to check out www.chemistry.org/periodic_table.html and homework.chem.uic.edu/NEXT.HTM#. For better understanding of fundamental organic chemistry, see chem.sis.nlm.nih.gov/chemidplus. Another course in human circulatory embryology (how the heart develops) is at www.indiana.edu/~anat550/embryo_main.

For the profile of how more than 1000 different types of receptors affect cell growth, cell division, transport of various small molecules, etc., look at www.receptome.stanford.edu/HPMR. For more on genetic pathways, “systems biology,” and signaling networks, check out www.genepath.org. And for understanding cellular functions via animation, www.johnkyrk.com.

Hosted by the Human Genome Variation Society (HGVS), which has been described in previous issues of *Interface*, is a site where one can directly deposit newly discovered mutations in human genes www.centralmutations.org. For the latest on human variation, see www.hapmap.org.

Wikipedia readers and writers have been writing and editing their own encyclopedia over the past 3 years. It now has more than 152,000 articles and everyone is invited to read these articles and/or contribute with something of their own. www.wikipedia.org.

Curious about the songs of various insects? See <http://buzz.ifas.ufl.edu>. Also photos, sketches of bug anatomy, range maps, and details of habits and insect habitats. And some beautiful photos of unique tropical wildflower and plant species and how they have evolved in Hawaii www.hear.org/starr/hiplants/index.html. A similar site, aimed at earth science and environmental science teachers is www.earthguide.ucsd.edu.

For understanding the public’s level of confidence in science, questions about science’s relationship with society, and such, look at www.psci-com.ac.uk/.

What is the origin of “beyond the pale?” (Folklore/proverbial expressions) “Pale” comes from a Latin word meaning “stake” or “boundary marker”. In the 16 century, the term, “English pale”, was used to describe areas under English dominion or jurisdiction. Check out this URL (I found it by asking Google “beyond the pale origin expression”). <http://www.yaelf.com/questions.shtml>

View the Milky Way at 10 million light years from the Earth. Then move (at powers of 10) through space towards the Earth in successive orders of magnitude until you reach a tall oak tree just outside the buildings of the National High Magnetic Field Laboratory in Tallahassee, Florida. After that, begin to move from the actual size of a leaf into a microscopic world that reveals leaf cell walls, the cell nucleus, chromatin, DNA and finally, into the subatomic universe of electrons and protons. <http://micro.magnet.fsu.edu/primer/java/scienceopticsu/powersof10/index.html>

brain cells come and brain cells go, but fat cells live forever

Latest in Genetics and Genomics, ...

What follows is a synopsis of the most interesting happenings during the last 6 months of 2003 with the Human Genome Project (HGP) and related genetics/genomics news, provided chronologically:

Jul 2003 Methodological flaws in the analysis of **18S ribosomal RNA** alignment have now been corrected [*Syst Biol* 2003; **52**: 283], showing that birds are evolutionarily related to crocodiles via a common reptilian ancestor.

More than 28,000 full-length cDNA clones from rice (*Oryza sativa*) have been collected, mapped, and annotated [*Science* 2003; **301**: 376]. The wheat and rice genomes have been compared [*Genome Res* 2003; **13**: 1818].

Aug 2003 “Paternal-age effect” disorders, such as achondroplasia and Apert syndrome, are disorders that occur more frequently in children of older men. The linear increase in the receptor tyrosine kinase gene *FGFR2* mutations with age was shown to confer a selective advantage to the sperm [*Nature* 2003; **422**: 297].

Genomes in the NIH pipeline to be sequenced include: chimpanzee (to be released before year’s end), chicken, honeybee, dog, cow, sea urchin, macaque, several fungi, pig, a single-cell ciliate (*Oxytricha trifallax*), and a flatworm [*Science* 2003; **301**: 1176].

A promising battery of tests has led to the tentative identification of a general learning ability, perhaps a means for measuring a mouse’s I.Q. [*J Neurosci* 2003; **23**: 6423; *Nature* 2003; **424**: 1004].

An excellent review on **horizontal gene transfer**, once believed to be frighteningly common and a major force that might interfere with accurate evolutionary analysis [*PNAS* 2003; **100**: 9658], now points out that HGT is likely to be relevant only to primitive genomes—modern organisms being constrained by selective barriers.

Sep 2003 An estrogen receptor ortholog was isolated from the mollusk *Aplysia californica* [*Science* 2003; **301**: 1714], confirming that sex steroid receptors are extremely ancient and wide-

spread—having diversified from a primordial gene before the origin of bilaterally symmetric animals, even though this gene was lost in the lineage leading to arthropods and nematodes.

Genes usually work together. Fights within the genome, pitting one gene against another, have been appreciated since the 1920s and it’s called “**meiotic drive**.” Many examples of these aggressive genes (called drivers) taking part in this intra-genomic conflict are described by E. Pennisi in *Science* 2003; **301**: 1837.

Treating with the powerful mutagen *N*-ethyl-*N*-nitrosourea (**ENU**) mice having a balancer chromosome (inversion of Chr 11) and then comparing genes conserved between mouse and human, researchers isolated 230 new recessive mouse mutations—defects in hematopoiesis, craniofacial and cardiovascular development, and fertility [*Nature* 2003; **425**: 81].

Sequencing his own poodle’s DNA, J. Craig Venter reports 80% completion of the dog genome and an estimated 18,473 dog genes that have human equivalents [*Science* 2003; **301**: 1898].

About 2% of genes in the human/mouse common ancestor (75 million years ago) have been deleted, or partially deleted, in the mouse. Other inversions, duplications and transpositions of >100 kb, comparing the two mammalian genomes, are discussed in detail [*PNAS* 2003; **100**: 11484; *Mamm Genome* 2003; **14**: 429].

The complete genome of a waterborne bacterium (*Chromobacterium violaceum*), which can cause fatal infections in humans, has been sequenced by the Brazilian National Genome Project Consortium [*PNAS* 2003; **100**: 11660].

Oct 2003 To determine the precise number of functional genes, researchers have tried to identify transcription units (open reading frame, **ORF**) combined with anti-sense knock-down experiments in *Arabidopsis thaliana* (tiny mustard). This approach has resulted in completion of ~30% of the *Arabidopsis* “ORFeome” as a resource for plant researchers and identification of 5,817 novel transcription units—above and beyond the ~25,500 genes already identified [*Science* 2003; **302**: 842].

The largest human chromosome sequenced to date (Chr 6) comprises 166,880,988 base pairs, 1,557 putative genes, and 633 pseudogenes [*Nature* 2003; **425**: 805, 775].

The South American grey short-tailed opossum (*Monodelphis domestica*) is now on NHGRI's short list of high-priority organisms whose genome will be sequenced [*Nature* 2003; **425**: 753]. The opossum surpassed the kangaroo as the first marsupial to be sequenced, to the chagrin of some Australians.

The evolution of 388 human olfactory receptor functional genes, divided into class I and class II and then latter further divided into 19 phylogenetic clades, has been elegantly detailed [*PNAS* 2003; **100**: 12235].

Nov 2003 In most textbooks, the single-cell eukaryote *Giardia intestinalis* (which causes diarrhea) has been regarded as a primitive intermediate, or "living fossil," because it possesses a nucleus but no mitochondria. *Giardia* has now been found to have tiny mitochondria, called *mitosomes*, that have an anaerobic function, essential for the assembly of Fe-S clusters [*Nature* 2003; **426**: 127, 172].

Comparative genomics is coming to the fore. By sequencing a second worm's genome (*Caenorhabditis briggsae*) and comparing it with that of the first worm (*Caenorhabditis elegans*), one can more accurately predict the correct number of functional genes [*PLoS Biol* 2003; **1**: 166].

The new revolution of **Systems Biology** is underway [*Genome Res* 2003; **13**: 2377]. Conserved co-expression can serve as an indicator of gene function on a genomic level.

To exploit the information within the human genome in the fight against cancer, more than 2 million expressed sequence tags (**ESTs**) from human tumors, and their corresponding normal tissues, have been deposited in public databases [*PNAS* 2003; **100**: 13418]. A cancer-oriented human transcriptome.

Is it possible to manufacture an organism, for example, tailored to degrade toxic waste dump sites or meet future fuel needs? J. Craig Venter announced some months ago that his Institute for Biological Energy Alternatives (Rockville, MD) was going to make their own bacterial virus; they then built a viral genome, from scratch, in 2 weeks' time and showed it could infect and kill bacteria just like normal phage viruses do [*Science* 2003; **302**: 1307]...!!

Dec 2003 A novel method for identifying functionally related genes, based on comparisons of neighborhoods in gene networks has been proposed [*Genome Res* 2003; **13**: 2568].

Starting with sources that include oocytes, blastocysts, and embryonic and adult stem cells, researchers have obtained 249,000 high-quality EST sequences, to produce an index of ~30,000 total mouse genes—including 977 previously not identified [*PLoS Biol* 2003; **1**: E74].

Coral (*Acropora millepora*), responsible for coral reefs, is an ancient member of the animal kingdom. DNA sequencing has revealed some genes in common with human genes [*Curr Biol* 2003; **13**: 2190].

Sequencing of the cow genome is now among the highest priority [*Science* 2003; **302**: 2050]. Co-evolution between cattle milk protein genes and human lactase genes has been shown [*Nat Genet* 2003; **35**: 311].

The chimpanzee (*Pan troglodytes*) genome draft sequence is now online [*Science* 2003; **302**: 1960]. The chimp is believed to be human's closest living relative, having diverged 5-6 million years ago. Genes for smelling, hearing and speech have undergone distinct, rapid changes whereas genes for the skeletal system (bones, muscle) have been less labile between chimps and humans. Of 7,645 shared genes, 1,547 human genes and 1,534 chimpanzee genes have experienced rapid changes—likely related to a survival advantage; interestingly, the human-accelerated genes are much more likely to underlie known major Mendelian diseases, e.g. the *PAH* gene for phenylketonuria.

A genome-wide survey of human alternative splicing suggests that **at least 74%** of multi-exon genes are alternatively spliced [*Science* 2003; **302**: 2141]...!! This is one means by which, say, 40,000 human genes might result in more than 100,000 transcripts that would then give rise to an even greater number of proteins.

 **Bob Hope** 
ON NEVER WINNING AN OSCAR

"Welcome to the Academy Awards or, as it's called at our home, 'Passover'."

Ethical, Legal and Social Issues, ...

Tidbits from the last 6 months of 2003:

Jul 2003 The U.S. Food & Drug Administration (FDA) is concerned about variability in adverse drug effects and is recommending that race and ethnicity data from clinical trials be collected, according to “five standard categories of skin color and/or country of origin” and “two categories of ethnicity.” The U.S. population is becoming increasingly diverse, however, with >6 million Americans reporting two or more races. Haga and Venter [*Science* 2003; **301**: 466] warn that: race and ethnicity data alone are insufficient, highly admixed populations cannot give clear results, and “individualized medicine” in the future is the only hope for trying to prevent adverse drug reactions.

Aug 2003 New Mexico’s Intelligent Design Network (IDnet-NM) tried to stir up the State Board of Education on public school science-teaching standards, with surveys that seemed dubious and actually might not have taken place [*Science* 2003; **301**: 1043].

Sep 2003 Coauthors J.T. den Dunnen and M.H. Paalman pose an imaginary scenario in which an XBG patient and his parents sued a clinical department, the XBG Mutation Database, and the journal *Human Mutation* because “serious and culpable mistakes were made during diagnosis of the pregnancy, leading to birth of an affected child.” From this, they emphasize the importance of standardizing the nomenclature of all gene mutations [*Hum Mutat* 2003; **22**: 181].

Oct 2003 The U.S. Senate approved the Genetic Information Non-discrimination Act of 2003 by a vote of 95–0, and the President signed this into law.

The National Institutes of Health (NIH) Roadmap [*Science* 2003; **302**: 63] defines a compelling set of priorities that can be acted upon, and are essential to accelerate progress across the spectrum of all the Institutes’ missions. There is considerable concern, however, that **investigator-initiated grants**—the engines that drive creative Nobel Prize-winning biomedical research—are in danger [*N Engl J Med* 2003; **349**: 2259] and that increasing amounts of money are being spent instead

on university infrastructure and Center- and Consortium-driven initiatives.

The Australian Law Reform Commission published their final report, *Essentially Yours: The Protection of Human Genetic Information in Australia*—which includes chapters on basic genetics, ethics, privacy law, genetic samples and testing, discrimination, informed consent, databases, tissue collections, genetic registers, genetic screening of populations, insurance, forensics, and many others.

Despite a suspected association between **aristocholeic acid** and cancer of the urinary tract, and the FDA issuing warnings in 2001 that herbal products containing aristocholeic acid are unsafe—these products are still available on the Web 2 years later [*N Engl J Med* 2003; **349**: 1576].

Nov 2003 Following 48,000 women in 12 cities through pregnancy and the first 7 years of their children’s lives, researchers found that in impoverished families, 60% of the variance in IQ is accounted for by the shared environment, and the contribution of genes is close to zero; in affluent families, the result is almost exactly the reverse [*Psychol Sci* 2003; **14**: 623]...!!

The FDA blocked the sale of the **AmpliChip CYP450**, which Roche developed with Affymetrix, stating that a “higher level of review is required, because it is of substantial importance in preventing impairment of human health,” and the DNA microchip “uses sophisticated technology” [*Science* 2003; **302**: 1134].

A case of newborn screening, potentially abnormal thyroid values, and when a physician should reveal information about a serious but avertable health risk to a relative of that patient—are reported in August [*N Engl J Med* 2003; **349**: 562], with follow-up comments in November [*N Engl J Med* 2003; **349**: 1870-72].

Dec 2003 There have been challenges in Kansas, Ohio, New Mexico, and now Texas. Fending off attempts (by the Discovery Institute and Texans for Better Science Education) to weaken references to “evolution,” the Texas State Board of Education approved a list of biology textbooks that scientists believe do justice to Darwinian evolutionary science [*Science* 2003; **302**: 1130].

BEST TYPO 2003
rumor suppressor gene

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

Tidbits from the last 8 months of 2003:

May 2003 Variation in 52 worldwide populations was studied at 377 autosomal short tandem repeat (STR) loci, to infer a demographic history of human populations. This well-written, scientifically solid article is *highly recommended reading* [*Am J Hum Genet* 2003; **72**: 1171].

Jul 2003 Defects in the *PPP3CC* gene, involved in calcium transport in the brain, might increase susceptibility to schizophrenia. Mice having this gene disrupted show symptoms similar to this disease [*PNAS* 2003; **100**: 8987].

Sep 2003 A candidate gene called *DYX1C1*, when disrupted, is implicated in developmental dyslexia (reading difficulty). The gene, which encodes a nuclear tetratricopeptide repeat domain protein dynamically regulated in brain, had mutations in a father and two daughters—as well as a number of other dyslexia patients, but not all dyslexia patients [*PNAS* 2003; **100**: 11553, 11190].

Discovery of a novel Y-chromosome variant suggests a very early occupation of the Americas about 30 to 40 thousand years ago, followed by a second wave ~13,000 years before the present [*Am J Hum Genet* 2003; **73**: 700].

Oct 2003 Comparing genes from Aboriginal, British, European Australian, and Bangladesh subjects, researchers found evidence for a gene flow across the Indian subcontinent towards Australia either ~90,000 years ago or ~60,000 years ago, and reaching widespread occupation 15,000 years later [*Science* 2003; **302**: 555]. Australia's national wild dog, the dingo, was found to have been introduced to that continent by a very small number of dogs originating in Southeast Asia [*Science* 2003; **302**: 555].

Impaired feedback regulation of the *XBPI* gene, pivotal in the endoplasmic reticulum stress response, appears to be a genetic risk factor for bipolar disorder [*Nat Genet* 2003; **35**: 171].

Loud unexpected noises make people blink, and the response can be dampened by prepulse inhibition (PPI). PPI is stronger in men than women, whereas homosexual men had PPI values closer to those of women and homosexual women had PPI

values closer to those of men [*Behav Neurosci* 2003; **117**: 1096]. A possible explanation is the level of testosterone exposure to the developing fetus in the womb—another example of the combination of genes (DNA makeup) and environment (in utero exposure).

The International **HapMap Project**, a 3-year \$100-million endeavor, proposes to produce a haplotype map based on similarities of block structure in European, African and Asian populations. The hope is to reduce the ~10 million common SNPs in the human genome to maybe 500,000 “tag-SNPs” representative of all 10 million SNPs [*Nature* 2003; **425**: 758; also **426**: 789]. Some are cautioning that this approach is too simplistic.

Nov 2003 Microsomal transfer protein (MCTP) is the rate-limiting step in lipoprotein synthesis and may affect longevity. Comparing 308 centenarians or people almost 100 years old in 137 extended families, researchers found significant linkage to an interval on chromosome 4, containing ~50 putative genes, and then identified a haplotype marker within the *MCTP* gene [*N Engl J Med* 2003; **349**: 1870-72].

Some high-frequency haplotypes have different alleles at every single-nucleotide polymorphism (SNP) site and are called **yin-yang**. Looking at 62 random human genomic loci and 85 gene-coding regions, Zhang and coworkers found 75-85% of the genome spanned by yin-yang haplotypes; they also found that 28 genomic loci in the fruit fly revealed a similar pattern [*Am J Hum Genet* 2003; **73**: 1073].

Genetic variation in a haplotype block spanning the insulin-degrading enzyme gene (*IDE*) has a significant effect on Alzheimer disease [*Hum Mutat* 2003; **22**: 363].

Looking at 8 kb of the dystrophin gene (*DMD*) in 1,343 chromosomes from around the world, researchers found one group that migrated out of Africa 27-56 thousand years ago, a second group that has never left Africa, and a third group that appears to have left Africa as early as 60 thousand years ago and then admixed with the other group that migrated out of Africa later [*Am J Hum Genet* 2003; **73**: 994].

Dec 2003 Linkage analysis in a large number of extended families in Iceland having low bone mineral density (osteoporosis), deCODE Genetics reported an association of this disease to the bone morphogenetic protein-2 gene (*BMP2*) on human chromosome 20p12 [*PLoS Biol* 2003; **1**: E69].

SCIENCE LITE

(low carbohydrate & low fat)

In the beginning God covered the earth with broccoli and cauliflower and spinach, green and yellow and red vegetables of all kinds, so Man and Woman would live long and healthy lives.

Then using God's bountiful gifts, Satan created Ben and Jerry's and Krispy Kreme. And Satan said, "You want hot fudge with that?" And Man said "Yes!" and Woman said, "I'll have another with sprinkles." And lo they gained 10 pounds.

And God created the healthful yogurt that Woman might keep the figure that Man found so fair.

And Satan brought forth white flour from the wheat, and sugar from the cane, and combined them. And Woman went from size 2 to size 14.

So God said, "Try my fresh green garden salad."

And Satan presented crumbled Bleu Cheese dressing and garlic toast on the side. And Man and Woman unfastened their belts following the repast.

God then said, "I have sent you heart healthful vegetables and olive oil in which to cook them."

And Satan brought forth deep fried coconut shrimp, butter dipped lobster chunks and chicken-fried steak so big it needed its own platter. And Man's cholesterol went through the roof.

God then brought forth running shoes so that his Children might lose those extra pounds.

And Satan came forth with a cable TV with remote control so Man would not have to toil changing the channels. And man and woman laughed and cried before the flickering light and started wearing stretch pants.

Then God brought forth the potato, naturally low in fat and brimming with potassium and good nutrition.

Then Satan peeled off the healthful skin and sliced the starchy center into chips and deep-fried them in animal fats and added copious quantities of salt. And Man put on more pounds.

God then gave lean beef so that Man might consume fewer calories and still satisfy his appetite.

And Satan created McDonald's and the 99-cent double cheeseburger. Then Lucifer said, "You want fries with that?" and Man replied, "Yes! And super size!" And Man went into cardiac arrest.

God sighed and created quadruple bypass surgery.

And then Satan created HMOs.

Amen

SCIENCE LITE (cont...)

If peanut butter cookies are made from peanut butter, then what are Girl Scout cookies made out of?

The biggest seller is cookbooks---and the second is diet books--how not to eat what you've just learned to cook." (Andy Rooney)

Don't name a pig you plan



to eat.

For those of you who watch what you eat...Here's the final word on nutrition and health. It's a relief to know the truth, after all those conflicting medical studies.

The Japanese eat very little fat and suffer fewer heart attacks than the British or Americans.

The Mexicans eat a lot of fat and suffer fewer heart attacks than the British or Americans.

The Japanese drink very little red wine and suffer fewer heart attacks than the British or Americans.

The Italians drink excessive amounts of red wine and suffer fewer heart attacks than the British or Americans.

The Germans drink lots of beer, eat lots of sausages and suffer fewer heart attacks than the British or Americans.

CONCLUSION: Eat and drink what you like, speaking English is apparently what kills you.

DAFFYNITION

Seamstress:

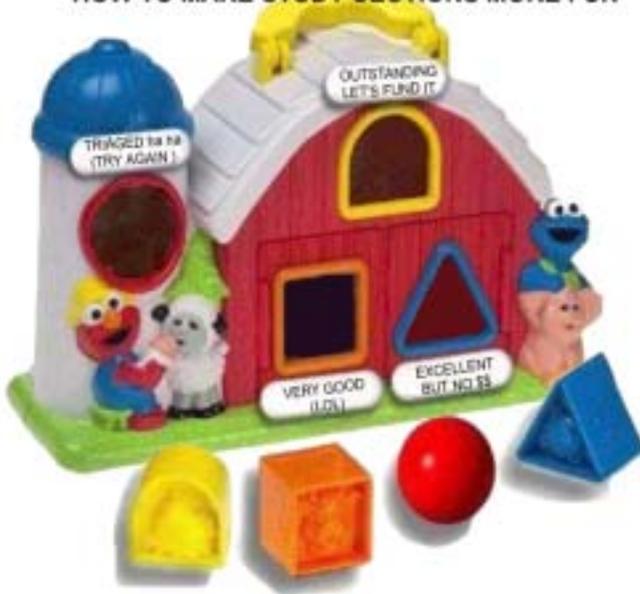
250 pounds in a size 6

Only in America

Suggested to the National Forest Service from a visitor to our nation's parks.

"Escalators would help on steep uphill areas of the hiking trails."

PROPOSED STUDY SECTION DEVICE
HOW TO MAKE STUDY SECTIONS MORE FUN



Concerning federal funding of your grant proposal, the "**Chaos Theory**" is the only one that can be used to predict whether you will be funded.

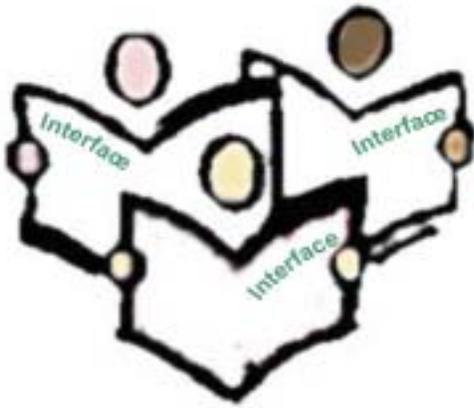
"Graduate students say the darndest things"

dramatic

recomblant

horoenzyme

ad-no-vice (adenovirus)



NEWS and EVENTS

COEP Functions July 2003-December 2003

COEP POSTER 2003 - Presented at the NIEHS
COEP Meeting, Baltimore, MD, October 2003

Health Literacy & Cultural Competency
An all-day workshop to promote the design &
development of effective
health-related educational materials
December 4, 2003

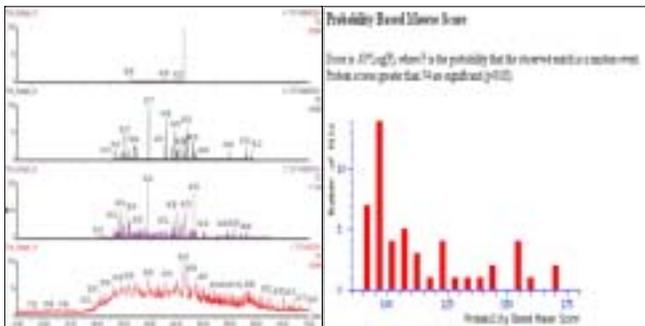
Kingsgate Marriott Conference Center
University of Cincinnati

Agenda and registration information was
accessed through the BROCHURE at
http://eh.uc.edu/ceg/COEP_brochure.pdf

A workshop luncheon,
"Proteomic Approaches & Data Analysis,"
sponsored by the Protein Analysis F&S Core
November 20, 2003, 10:00 am to 1:00 pm
Room 121 of Kettering Lab.

Over 40 colleagues and students attended.
Pat Limbach's presentation: "Characterizing
protein modifications and protein-protein
interactions by mass spectrometry"
can be viewed at

http://eh.uc.edu/ceg/Limbach_CEGWorkshop_MSPF.pps



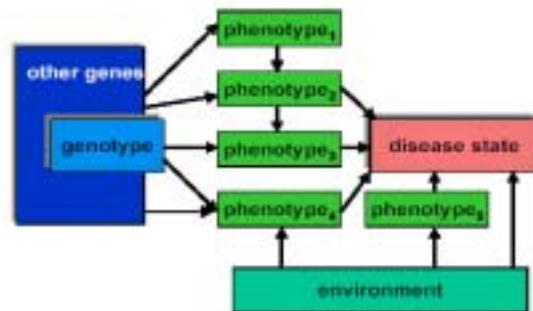
A Special Seminar, sponsored by the
Human Populations Core September 10th 2003;
2:00 pm, Room 121 of Kettering Lab.

Dr. Partha P. Majumder, Prof.,
Chair of Human Genetics
Indian Statistical Institute, Calcutta, India

"Complex disease: approaches to dissection"

If you missed the lecture, go to
http://eh.uc.edu/ceg/Majumder_seminar.pdf
for a powerpoint presentation.

Complex Disease Genetics



A workshop and luncheon,
sponsored by the Genomics F&S Core
September 3rd, 2003.

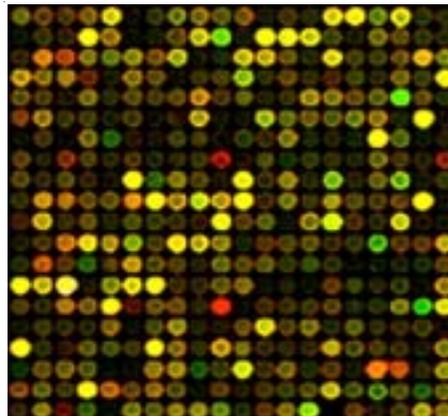
"Members' Feedback on Microarray Core Services"

Several CEG members described their
projects and their experiences using the Core.

Presenters were :

Aronow, Belcher, Doetschman, Puga,
Tomlinson and Medvedovic.

Attendance was more than 30.



Interface is supported by NIH grant # ES06096 from the National Institute of Environmental Health Sciences, and is published by the Center for Environmental Genetics, **Marshall Anderson, PhD, Director**

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IGenes 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

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CEG Members in the News

Sohaib Khan organized the Jensen Symposium, which attracted about 350 attendees from around the world (Dec 03).

Mary Beth Genter was invited by the American College of Toxicology to present a lecture entitled "*Molecular biology of the nasal airways: How do we assess cellular and molecular responses in the nose?*" at their annual meeting in Washington, DC (Nov 04).

Dan Nebert was invited to write a review for *Clinical Genetics*, specifically titled "Pharmacogenetics and pharmacogenomics: why is this relevant to the clinical geneticist?" Since the review appeared (Oct 99), it has become recommended reading for anyone planning to take the American Board of Medical Genetics recertification exam. **Nebert** was also invited to present a Keynote Address at the 9th International Congress on Toxicology (ICT IX; Jul 01), specifically titled "Transcription factors and cancer: an overview," which was published as a review (Dec 02) in *Toxicology*. This paper has been among the "10 top down-

loaded articles of all articles published in Elsevier journals" during the first half of 2003. **Nebert** was also invited to give the Plenary Lecture during the Session on Human Genomics, at the International Symposium of the Pacific Rim Association of Clinical Pharmacogenetics (PRACPG), Los Angeles, California (Nov 03).

Nancy Warren made invited presentations at Marshall University, Huntington, WV, (Aug 03); at the National Society of Genetic Counselors meeting Charlotte, NC, (Sep 03); and at the Association of Schools of Allied Health meeting, Toronto, Canada, (Oct 03).

Peter Stambrook was voted President-elect of the Environmental Mutagen Society. He also served on the Planning Committee for an EU-US workshop on Molecular Signatures of DNA damage-induced Stress Responses that was held in Cortina, Italy (Sep 03) and was an invited speaker at the International Antimutagenesis Conference held in Pisa, Italy (Oct 03). **Stambrook** organized a symposium sponsored by the NIEHS entitled, "*Haplotypes, SNPs and Disease.*" (Dec 03).