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NTERFACE:

GENES AND THE ENVIRONMENT

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Everything you Always Wanted to Know about Dioxin but Were Afraid to Ask

Since the alleged dioxin poisoning of ***Viktor Yushchenko*** during a political dinner on 5 Sep 2004, and now that he won the 26 Dec 2004 election in the Ukraine with 52% of the vote, many questions are being asked about dioxin. A number of laboratories in the CEG have carried out dioxin research for many years. "Dioxins" is a general term describing a group of 72 chemicals that are highly persistent in the environment**;** the term is also applied to 15 or 20 "dioxin-like compounds" (**DLCs**) that include the co-planar polychlorinated biphenyls (**PCBs**). Their chemical structures are such that they are degraded with great difficulty—whether it is by bacteria, plants, fungi, animals, or by simple sunlight photooxidation. Dioxins are best degraded at very high temperatures (incineration). This means that dioxins enter the food chain (plants, agricultural animals, fish, etc.) and ultimately wind up in humans who eat these foods. Because of their persistence, these dioxins are stored in the fat tissues of everyone's body. Dioxins are present even in penguins and polar bears that live far from the sources of production of these chemicals (however, ocean currents carrying plankton, fish and other marine animals do reach the arctic and antarctic regions, where these predators eat them).

Chemistry

For the chemists among you, the most potent of the dioxins is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (**TCDD**; **Figure 1**). This molecule has "3-plane symmetry"**;** also, there are no adjacent carbon atoms that are free of chlorine atoms, meaning that epoxidation or hydroxylation across a carbon-carbon double bond by an enzyme is virtually impossible. Dioxins are formed as an incidental byproduct of many industrial processes involving the high-temperature combination of phenols and chlorine—such as waste incineration, pulp and paper bleaching, synthesis of hexachlorophene soap, chemical and herbicide manufacturing—and even forest fires.

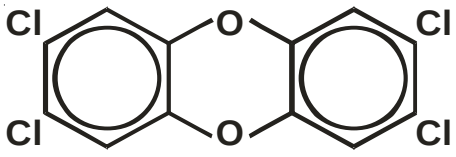

Fig. 1. Chemical structure of TCDD

Environmental Contamination

Vietnam. Although present at 1% or less, TCDD is the primary toxic component of ***Agent Orange***, the principal herbicide sprayed in Vietnam (more than 19 million gallons between 1961 and 1971). Agent Orange is a "super-agonist" of the

IN THIS ISSUE

Everything about Dioxin....1
Latest in Genetics and Genomics....4
Writing Recommendation Letters....5
Biotechnology....6
Ethical, Legal and Social Issues....6
Evolutionarily Speaking....7
Gene-Environment Tidbits of Interest....9
Observations by a Biologist....10
Letters to the Editor....11
CEG Members in the News....12
Only in America....13
Web-Cytes....13
Science Lite....14
Human Variation, Disease, Migration and Evolution....15
Genetic Issues on Race....17
"Q"uote of the Month....18

normal plant hormone ***indoleacetic acid*** (**IAA**), which speeds up the process of leaf growing, thus resulting in the rapid defoliation of trees.

Love Canal. TCDD contamination was the problem at Love Canal (near Niagara Falls, NY). This canal began in 1892, when William T. Love proposed digging a canal to connect the upper and lower parts of the Niagara River**;** the canal was never completed. Hooker Chemical and Plastics Corporation purchased the property and, between 1947 and 1954, they deposited an estimated 20,000 tons of "high-level toxic waste" into the concrete-lined canal. A total of 248 assorted chemicals were buried at the site, including**:** the pesticide hexachlorocyclohexane, chlorobenzenes, chlorinated hydrocarbons, benzene, chloroform, trichloroethylene, methylene chloride, benzene hexachloride, phosphorous, and PCBs. In addition, it is estimated that about 130 pounds of dioxin were buried in Love Canal. The canal was covered with dirt in 1953, and most people presumed it was "safe". Residents in the area, however, began to report foul odors and health problems between the mid 1950s and mid 1970s, and the previous dumping of hazardous waste was then investigated. Government officials decided that Love Canal was a health hazard, and the area began to be evacuated (1978-80). The problems at the Love Canal played an important role in Congress establishing the Superfund Basic Research Programs (see issue #27 of ***Interface***). In 1980 Congress passed *the Comprehensive Environmental Response, Compensation, and Liability Act* (**CERCLA**) [Public Law 96-510], commonly known as ***Superfund***, which required EPA to locate all contaminated sites in the U.S., establish priorities for cleaning them up, and then clean them up. Since 1980, Superfund began to clean up the Love Canal. As a result, people began moving back to Love Canal in the early 1990s. Many of the homes have been renovated and resold to new citizens (at much lower rates than that of other surrounding communities), and the region is gradually moving back to normal.

Times Beach. TCDD was also the cause of the evacuation (1983-85) of Times Beach, a small town 17 miles southwest of St. Louis, Missouri. In this case, dioxins were present in a mixture of "dust-controlling oil", made out of chemical waste by Northeast Pharmaceutical and Chemical Company (NEPACCO), which had produced Agent Orange during the Vietnam War. In 1971, thousands of gallons of this oil were sprayed on the unpaved roads (and in horse stables and race tracks) of Times Beach. Just a few days after the oil had been sprayed, animals in the area began dying**;** a few months later, children with illnesses began to be reported. By 1981, about 75 horses, and an unknown number of dogs, cats, chickens, rodents and birds had perished, and some scientists were recommending that people evacuate the area. In Nov 1982, soil tests had confirmed that high levels of dioxin were poisoning the town. In Feb 1983, US$33 million of Superfund money was used to purchase Times Beach and relocate the people. The town was officially closed in Apr 1985. About 265,000 tons of contaminated soil and debris from Times Beach, and 28 other sites in eastern Missouri, were burned at high temperatures (between Mar 96 and Jun 97) in an incinerator built and operated on the site by Syntex, the parent company of NEPACCO. The cleanup cost the government a total of US$110 million—$10 million of which was reimbursed by Syntex. After the cleanup, the incinerator was dismantled and the site was turned over to the State of Missouri. The site of Times Beach now houses a wild-bird sanctuary, a 409-acre state park commemorating ***Route 66*** (the famous highway that stretched from Chicago to Los Angeles, passing near this community) and a small museum detailing the "environmental history" of the area.

Seveso. TCDD was also the cause of problems in Seveso, Italy. A chemical plant in Italy was producing ***hexachlorophene*** (an antiseptic soap), of which TCDD is a byproduct**;** an explosion at this site on 10 Jul 1976 caused a large cloud, which began settling on the streets and buildings of the small village. Children who played in the cloud "because it looked like snow" developed burns on their skin**;** after a few weeks some developed ***chloracne*** on their faces and other skin areas exposed to the chemical cloud. Chloracne is a bad case of pimples, caused by abnormal growth of sebaceous (sweat) glands in the skin. This is the condition that can now be seen on the face of Viktor Yushchenko.

Again, animals dying on the streets of Seveso, in those next several days following the blast, were more of a harbinger of the toxic effects of that cloud

than the children suffering a few superficial burns on their skin. Follow-up studies of the exposed Seveso human population 20 years later have found no highly significant increases in birth defects or cancer, but—intriguingly—a significantly increased risk in certain types of heart disease. Problems with TCDD-induced arteriosclerosis have also been found in laboratory animals.

Disclaimer

In any of these four locations (Vietnam, Love Canal, Times Beach, Seveso), TCDD was not the sole contaminant**;** rather, there was always a mixture of persistent organic pollutants and DLCs. Hence, it is impossible to conclude that the medical problems seen in any of these locations were caused specifically by TCDD intoxication.

High-Dose TCDD Toxicity

In contrast to these "relatively large-dose exposures" via contaminated land, water or air (described above), what might happen with the sudden ingestion of an even higher, sudden dose of TCDD? Acute toxicity in laboratory animals peaks between 7 and 30 days, and pretty much subsides by 8 weeks. If death is going to occur, it usually occurs between 28 and 35 days—probably associated with suppression of the immune system and bone marrow. This lab-animal scenario seems to have been the course of Yushchenko's illness**:** he had abdominal cramping the night after the alleged poisonous meal, he was most ill in October, and now he has continued to get better with time. His face is still heavily pocked, and it is not clear if the effects of his chloracne will ever be completely reversible. As far as is known, no human has ever died acutely from a TCDD overdose.

With an *estimated dose of 25 micrograms per kilogram body weight*, Yushchenko might have consumed 2 to 3 milligrams of TCDD at that dinner**;** at the current listing of US$81 for 10 micrograms of TCDD (from Sigma Chemical Company), this alleged attempt at poisoning would have cost someone between US$16,000 and US$25,000 (unless a government lab synthesized this for the explicit purpose of trying to poison someone). This approximation is, of course, a rough estimate, and the dose might have been ten times higher. Interestingly, for whatever reason, humans seem to be far more resistant to dioxin-induced lethality than most animals—as witnessed by animals dying in the streets of Love Canal, Times Beach, and Seveso whereas humans suffered milder effects later.

Long-Term TCDD Toxicity

Long-term effects of TCDD in humans include an increased risk of**:** cardiovascular disease, skin disorders (especially the chloracne, as described above), soft-tissue cancers, and certain types of leukemia. These two latter diseases (different forms of malignancy) are epidemiologically not well established, because—among other reasons—there is no specific target organ or cell type. In 1997 the International Agency for Research on Cancer (**IARC**; based in Lyon, France) classified TCDD as a "Class I carcinogen"—meaning that it is a "known human carcinogen." However, TCDD is the only compound that has been classified by IARC as a human carcinogen without a well-established target organ or cell type. The EPA reassessment of TCDD as a carcinogen is underway, with their conclusions expected to be reported during 2005.

Long-term effects of TCDD in laboratory animals, as with humans, also include an increased risk of heart disease, skin disorders (sebaceous gland overgrowth, manifested as chloracne in humans), soft-tissue cancers, and certain types of leukemia. Other maladies caused by TCDD in lab animals but not yet proven in humans (due to difficulties in epidemiologic studies) include**:** endometriosis (issue #17 of ***Interface***), lowered fertility (low testosterone levels and reduced sperm counts), birth defects (in children of parents exposed), diabetes, learning disabilities, lung problems, and endocrine disruption (at least in some animals, such as the rat, there is demasculinization of males). Endometriosis is a disorder in which the lining of the uterus is found in locations outside the uterus**;** it is the most common cause of pelvic pain in women and a cause of infertility. Female rhesus monkeys on very low exposure levels to TCDD have been shown to develop endometriosis. Because TCDD toxicity is not an all-or-none effect but rather simply "increases one's risk," it is extremely difficult (in a court of law) to attribute any particular medical problem exclusively to prior dioxin exposure.

Possible Treatment of Dioxin Poisoning?

Can anything be done to treat a large overdose and/or a high body burden of TCDD? Until recently it

was believed that nothing could be done—except to allow the poorly-degradable chemical to leave the body slowly, with a half-life of more than 7 years. Recent studies (by Paul Tso and Ron Jandacek, University of Cincinnati, Department of Pathology), however, have shown that body burdens of very poorly-degradable chemicals (such as dioxins and PCBs) can be treated successfully with ***olestra*** and olestra-like compounds (sucrose polymers that pass through the gastrointestinal tract without being absorbed)**;** coincidentally, olestra "pulls out" these highly fat-soluble chemicals, enabling the chemicals to be excreted in the stool. We would hope that Yushchenko is being treated in this way.

Olestra-containing foods include "fat-free" versions of *Pringles*, *Lays' Potato Chips*, *Ruffles*, *Doritos*, and *Tostitos*. These foods have the unfortunate side-effects (at least, in some susceptible people) of diarrhea, cramps, and even bleeding.

—Contributed by Dan Nebert; reviewed by Alvaro Puga

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 2004 with the Human Genome Project (**HGP**), and related genetics/genomics news, provided chronologically**:**

Jul 2004 RNA interference (**RNAi**) has been discussed in many past issues of ***Interface***, but there is a wonderful review in *Nature* 2004; **430:** 161. Definitions of short-interfering (**siRNAs**), micro (**miRNAs**), tiny non-coding (**tncRNAs**) and small modulatory (**smRNAs**) are given. Not only has RNAi become a powerful laboratory tool (one can knock down each gene of an organism's genome and test each mutant on DNA chips), but RNAi is a widespread natural phenomenon occurring probably in all plants and animals.

The human genome has an estimated 11 million single-nucleotide polymorphisms (**SNPs**) occurring at frequencies of 1% or greater. Sequencing of 15 loci **in maize** (*Zea mays*) hybrids indicates that this little corn plant has the **number of SNPs** an order of magnitude greater than that of human [*Plant Cell* 2004; **16:** 1707]**..!** This might be why agricultural corn has improved so quickly, due to selective breeding.

It is well known that the aryl hydrocarbon receptor (**AHR**) regulates many genes by binding to the AHR response element (**AHRE**) in their regulatory regions. Now a second DNA motif has been discovered [*BBRC* 2004; **321:** 707]—meaning that the latter should be named **AHRE2**.

Aug 2004 After identifying all genes in a genome, one needs to identify all expression patterns to understand systems biology. A first version of the *Caenorhabditis elegans* (roundworm) "**promoterome**" has now been offered [*Genome Res* 204; **14:** 2169], which can be combined with open reading frames (**ORFs**) available in "**ORFeome**" resources (described in previous issues of the ***Interface***).

Sept 2004 The DNA sequence and comparative analysis of human chromosome 5 is now completed [*Nature* 2004; **431:** 268]. It is one of the largest chromosomes, yet has one of the lowest gene densities. In total, 923 manually-curated protein-coding genes [including the protocadherin (*PCDH*) and interleukin (*IL*) gene families] were compiled.

Cryptic genetic variation (**CGV**) is not normally seen, very much underappreciated, not at all understood, but is an essential source of physiological and evolutionary potential [*Nat Rev Genet* 2004; **5:** 681]. CGV occurs when an organism is stressed by environmental pressures and probably helps explain certain complex diseases seen clinically. For example, CGV *somehow* allows a synonymous mutation (*i.e.* no amino-acid change) in the *Drosophila Egfr* gene on one chromosome to override the dominant phenotype on the other chromosome [*Curr Biol* 2003; **13:** 1888].

Oct 2004 The Human Gene Nomenclature Committee (HGNC) Database was pleased to announce on Friday, October 15th, http://www.gene.ucl.ac.uk/nomenclature/, that they had now approved **20,001 gene symbols**, thereby breaking the magic "20,000-gene barrier".

Using a maskless photolithography method to produce microarrays of the entire fruit fly genome [*Science* 2004; **306:** 655], **differential splicing** of about 40% of predicted genes was found. This compares to an estimated >70% of alternatively spliced protein-coding genes in the human genome.

Is it possible that active genes (distal from one

another, in the sense of chromosomes) migrate in the nucleus to preassembled transcription sites, where such gene expression activity is turned up? Evidence for such "**transcription factories**" is presented [*Nat Genet* 2004; **36:** 1065].

The *Drosophila* gene *Dscam* (Down syndrome cell adhesion molecule) encodes an axon-guidance protein. The DSCAM transcript undergoes a remarkable degree of **alternative splicing**—resulting in perhaps as many as **38,016** different proteins [*Cell* 2004; **118:** 619]**..!**

The **human genome's DNA sequence** was ~97% completed in 2001, and now it is perhaps ~99% completed [*Nature* 2004; **431:** 927]. **Build 35** contains 2.85 billion bases interrupted by only 341 gaps [*ibid*, p 931]. Segmental duplications (in each individual's genome) must be resolved, however, because they show high transcriptional content, they are associated with disease and large-scale copy-number polymorphisms, and have played an important role in the chromosomal evolution of mammalian genomes.

Nov 2004 The microRNA (***miRNA***) genes, which are about 1% as abundant as all human genes, appear to regulate protein production of about 10% or more of all human genes [*PLoS Biol* 2004; **2:** e363].

Using **RNAi** analysis in *Drosophila*, 47 proteins were identified as **splicing regulators**, 26 of which had not previously been implicated in alternative splicing [*PNAS* 2004; **101:** 15974].

"GeneFinder" programs of course are designed to identify the **translation start-site** of proteins with the ATG initiation codon. This could be a problem if the translation initiation starts with CUG for leucine [*PLoS Biol* 2004; **2:** e366]**..!**

Dec 2004 There are three nuclear factor (erythroid-derived 2)-like genes in the human genome**:** *NFE2L1*, *NFE2L2* and *NFE2L3*. Their previous unofficial names were Nrf1, Nrf2 and Nrf3, but this "NRF" root and series had to be changed—due to the earlier official designation of nuclear respiratory factor-1 as the *NRF1* gene. The electrophile-response-element (EPRE)-binding NFE2L1 and NFE2L2 factors are known to up-regulate a battery of defensive genes in response to oxidative stress**;** NFE2L3 is now suggested to be a negative regulator, also binding to the EPRE [*J Biol Chem* 2004; **279:** 50810].

"If a person isn't liberal at 20, he has no heart, and if he isn't conservative by the time he's 40, he has no brain."
- Winston Churchill

It's that time of year when we are asked to write recommendations!

Robert Thornton, a professor of economics at Lehigh University in Bethlehem, PA, was frustrated about an occupational hazard for teachers, *i.e.* having to write letters of recommendation for people with dubious qualifications, so he put together an arsenal of statements that can be read two ways.

You're called upon for an opinion of a friend who is extremely lazy:
"In my opinion, you will be very fortunate to get this person to work for you."

To describe a person who is totally inept:
"I most enthusiastically recommend this candidate with no qualifications whatsoever."

To describe an ex-employee who had problems getting along with fellow workers:
"I am pleased to say that this candidate is a former colleague of mine."

To describe a candidate who is so unproductive that the job would be better left unfilled:
"I can assure you that no person would be better for the job."

To describe a job applicant who is not worthy of further consideration:
"I would urge you to waste no time in making this candidate an offer of employment."

To describe a person with lackluster credentials:
"All in all, I cannot say enough good things about this candidate or recommend him too highly."

Biotechnology, ...

Tidbits during the last half of 2004, concerning genetically-modified (**GM**) plants, biotechology, and related topics**:**

Jul 2004 **T cell-derived cytokines** are important in the development of an effective immune response, but, when dysregulated, they can promote disease. A new cytokine, **interleukin-31** (IL-31), was identified, which is preferentially produced by T helper type-2 cells. IL-31 signals through a receptor composed of IL-31 receptor A and oncostatin M receptor. Using transgenic mice that overexpress IL-31, it was found that IL-31 appears to be involved in mediating dermatitis and hyperresponsive airway disease [*Nat Immunol* 2004; **5:** 752].

Aug 2004 Many laboratories use **firefly luciferase** (***LUC***) bioluminescence as a **reporter gene**—in cells, tissues and intact animals. **Lipoic acid** has an inhibitory effect on LUC expression [*BBRC* 2004; **323:** 625], which might need to be considered in the interpretation of various experimental results using the *LUC* reporter gene.

Sep 2004 Microarray data need to be standardized across the world, as discussed previously in ***Interface***. Experiments should adhere to the "Minimum Information about a Microarray Experiment" (**MIAME**) [*PloS Biol* 2004; **2:** e317].

Medulloblastomas (a common childhood brain tumor) and some other cancers have a **defect in the sonic hedgehog (*SHH*) pathway**. In mice having medulloblastomas, an inhibitor of the SHH signal transduction pathway was able to shrink these tumors and allow the mice to stay tumor-free for longer periods of time [*Cancer Cell* 2004; **6:** 229]. The hope is that such compounds can be used to treat these types of cancer**;** however, many compounds—targeting different cell-growth pathways in various tumor types—will probably be necessary.

Oct 2004 Clinical pharmacology is always fraught with the dangers of walking on a tightrope. When a drug helps one system (or set of diseases), it could be making something else worse. This summarizes the "**cyclooxygenase-inhibitor** story" [*Science* 2004; **306:** 384; *N Engl J Med* 2004; **351:** 1709], in which **Vioxx** (for treatment of arthritis) has been withdrawn from the market (because of increased risk of blood clots and heart disease). Similar drugs are likely to follow (being accused of increasing one's risk of heart disease), but, hey, isn't this simply the Story of Life**:** "what is one man's meat is another man's poison".

Nov 2004 **Telomeric length** is a crucial factor in normal chromosomal function and senescence. Now, the DNA helicase *DDX11* gene has been shown to participate in the regulation of telomere length [*Am J Hum Genet* 2004; **76:** 147]. This finding could lead to a better understanding of chromosomal assembly, telomere biology, and age-related diseases.

Ethical, Legal and Social Issues, ...

ELSI tidbits from the last 6 months of 2004**:**

Jul 2004 Using a stable hepatoma cell line to express the human pregnane X receptor (**PXR**), it was shown that organochlorine, organophosphate and pyrethroid pesticides are able to activate the human *CYP3A4* and *CYP2B6* genes via the PXR [*Biochem Pharmacol* 2004; **68:** 2347]. This is another piece of evidence that **pesticide exposure** can affect some people's rates of metabolism of certain **prescribed drugs**.

Some have advocated the **prescribing of drugs based on "race"**. However, the use of "race" as a biological variable is problematic [*Am J Pharmacogenomics* 2003; **3:** 385]. And it now appears likely that the pattern of heterogeneity "across the entire planet" will be one of **gradients of allelic frequencies** rather than finding any major genetic discontinuities on different continents [*Genome Res* 2004; **14:** 1679].

Sep 2004 From the Discovery Institute in Seattle WA comes a paper arguing that the complexity of living organisms cannot be explained by Darwinian evolution [*Proc Biol Soc Wash* 2004; **117:** 213]. This paper was regarded by advocates of **creationism** and **intelligent design** as a "breakthrough" publication of this point-of-view in a scientific journal. Opponents insist that "peer review is not a guarantee of accuracy, and this is especially true of review articles" [*Nature* 2004; **431:** 114].

Next-Best typo 2004 "polypeptied"

Oct 2004 The most likely explanation for the **"Gulf War Syndrome"** (fatigue, muscle and joint pain, memory loss, dizziness) is the effect of **neurotoxicants** [*Science* 2004; **306:** 26]. Since the nervous system and immune system are intimately linked, this makes sense. In issue #1 of *Interface*, we had discussed the possibility that genetic variations in the *PON1* gene might reflect interindividual differences in one's risk for the Gulf War Syndrome (given the same exposure to any two soldiers to whatever toxicant in the war zone). That possibility continues to be feasible and is consistent with these latest conclusions.

Just in case you need to see a graph, proving the point that the **NIH budget** has more than doubled since 1999 while the total number of **R01 applications** has remained constant or slightly fallen, this problem is addressed [*J Clin Invest* 2004; **114:** 872]. Obviously, the biggest problem is that, throughout history, the major contributor to almost all novel breakthroughs in U.S. biomedical research has been, of course, the individual lab funded by the R01 mechanism.

Nov 2004 The addition of isosorbide dinitrate and hydralazine to conventional therapy for heart failure decreased the relative 1-year mortality rate by 43% among African-Americans [*N Engl J Med* 2004; **351:** 2049 & 2035]. This report will generate a lot of interest. What if an African-American's genes responsible for this therapeutic improvement actually carry Caucasian alleles? African-Americans have, on average, 26% Caucasian alleles—with higher rates in the Chicago-to-New-Orleans corridor [*Hum Genet* 1999; **104:** 109].What if a European-American's genes responsible for this improvement are actually African alleles? Elsewhere in this issue (see "Human Variation"), it is reported that a single gene (*MC1R*) is responsible for all shades of skin color. It therefore becomes problematic when one begins to choose drug therapy, based on what ethnicity the person "seems" to be.

PARADOX –
if you choose to do nothing, you'll never be finished

Evolutionarily Speaking, ...

What follows is a synopsis of some of the more interesting things that have happened during the last 6 months of 2004 with the Human Genome Project (**HGP**), and evolutionarily-related news, provided chronologically**:**

Jul 2004 "**Horizontal gene transfer**"(**HGT**) occurs when a gene from one organism is "captured" and put into the genome of another organism; past issues of ***Interface*** have described this in detail, since many were worried that HGT would mess up phylogenetic trees. It now appears clear that HGT is limited pretty much to different bacteria [*Science* 2004; **305:** 334]. For example, about 25% of the genome of the common intestinal bacterium, *Escherichia coli*, has been "acquired" from other species.

What is the **world's smallest and lightest-weight vertebrate?** The stout infantfish, or *Schindleria brevipinguis*, averages 7 mm in length—with pregnant females ~8.4 mm and weighing 1 mg. Adults retain larval characteristics, have no teeth or scales, and contain no pigment except in the eyes [*Science* 2004; **305:** 472].

Aug 2004 The previous conclusion that "chromosomal rearrangements played a key role in **human-chimpanzee speciation**" now appears not to be the case [*Genomics* 2004; **84:** 757]. The confounding factors of limited sample size, nonuniform distribution of genes, and stochastic noise (chaos) in substitution rates—suggest that bioinformatic surveys must be carried out with great caution.

Sept 2004 In yeast, calorie restriction activates *SIR2* and increases life span. Disruption of the *FOB1* gene decreases extrachromosomal ribosomal DNA circles (**ERCs**) and enhances the reproductive life cycle. Deletion of both the *FOB1* and *SIR2* genes act in parallel pathways to **promote longevity** [*PLoS Biol* 2004; **2:** e296]. Can these data be extrapolated to longevity in mammals?

High school kids learn that there are 64 possible codons (triplets of 3 bases in mRNA) that encode the 20 essential amino acids by way of 20 universal aminoacyl tRNA synthetases—one for each amino acid. In certain *Archaebacteria*, however, there is **a 21st amino acid** (pyrrolysine) encoded by UGA (normally a stop codon) via a 21st aminoacyl tRNA synthetase [*Nature* 2004; **431:** 333]. Selenocysteine is another example of an unusual **22nd amino acid**

[*PNAS* 2004; **101:** 13395], encoded by UGA via a special elongation factor, SelB, that binds to the selenocysteine-loading tRNA [*Mol Cell Biol* 2002; **22:** 3565].

There are ten **bone morphogenic protein** genes (*BMP1* to *BMP10*) in the human genome, and defects in BMP2 are associated with increased risk in osteoporosis [*Growth Factors* 2004; **22:** 233]. Now it turns out that BMP4 is important in the developmental formation and shape of **the beak** in chickens, ducks and finches [*Science* 2004; **305:** 1462 & 1465].

Oct 2004 Recent work suggests that sequence diversity in a 648-bp region of the mitochondrial gene, cytochrome *c* oxidase (*MT-CO1*), might serve as **a bar code** for the **identification of animal species**—including mammals and birds [*PLoS Biol* 2004; **2:** e312].

Diatoms are single-celled algae (containing plastids and encased in silica) and are responsible for ~20% of all carbon fixation in the world. They are eaten by marine animals, including the whale. Now the 34.5-Mb genome has been sequenced**:** it contains ~11,500 genes—including some needed for **silicic acid** transport and formation of their **silica**-based cell walls [*Science* 2004; **306:** 79].

Conserved nongenic sequences (**CNGs**) were described in the last issue of ***Interface*****;** they do not encode any protein, are on average about 520-540 bp in length, sometimes exist near genes but often are located in "gene-desert" regions, and are nearly 90-100% conserved across species as diverse as human and *Takifugu rubripes* (puffer fish). Deleting two large segments (845 kb and 1,511 kb) of "gene-desert" DNA in the mouse that harbored 1,243 CNGs, only minor differences in expression patterns were seen [*Nature* 2004; **431:** 988]—thus keeping it a mystery as to the function of these highly conserved nongenic sequences.

Nov 2004 The **duck-billed platypus** (marsupial in Australia) has been an enigma, as far as its **karyotype** (chromosomal configuration). Now the 52-chromosome total has been resolved**:** there are 21 pairs of autosomes and TEN sex chromosomes (5 X and 5 Y), and the ten sex chromosomes are linked by homologous regions as a 10-membered circular chain during meiosis [*PNAS* 2004; **101:** 16257], sharing genes with the bird Z and mammalian X chromosomes [*Nature* 2004; **432:** 913]**..!**

Modern **head lice**, *Pediculus humanus*, originated from two ancient lineages ~1.18 million years ago**;** there was a recent population bottleneck (~100,000 years ago). If these two louse species codiverged with their *Homo* hosts more than a million years ago, then a recent host switch is required to explain the occurrence of both lineages on modern *H. sapiens*—suggesting that there must have been some direct physical contact between **archaic and modern forms of humans** [*PLoS Biol* 2004; **2:** e340].

Dec 2004 A **dense SNP map** has been generated for *in silico* mapping **in the mouse** [*PLoS Biol* 2004; **2:** e393]**:** 10,990 evenly-spaced SNPs were established across 48 inbred mouse strains. A haplotype refers to the pattern (relationship of one to another) of DNA variant sites, along one chromosome. Unique patterns, within blocks of three SNPs as an inferred haplotype, could successfully map known single-gene traits and a cloned quantitative trait gene.

From the evolution of drug resistance to the phenomenon of cancer progression, "**adaptive mutation**" represents the availability of alternative pathways for genetic or evolutionary adaptation and clonal expansion in organisms that are being **subjected to stress**. The most-well-studied model is the starvation of stationary-phase *E. coli* cells on lactose medium that induces Lac^+ revertants at frequencies higher than that predicted by usual mutation models [*PLoS Biol* 2004; **2:** e399]. Adaptive mutation is not the same as cryptic genetic variation [see Sept of "Genomically" in this issue].

The **parathyroid gland**, derived from the pharyngeal pouch endoderm, is controlled by a key regulatory gene, *GCM2*. Following expression of this gene [*PNAS* 2004; **101:** 17716], it was determined that the parathyroid gland likely came into being as a result of the transformation of fish gills during evolution of the tetrapod (4-legged animal).

How did the **human brain** evolve so quickly, to distinguish us from other primates or mammals? Higher rates of protein evolution in primates were found for 9 developmental genes, 9 physiological genes, and 6 unclassified genes [*Cell* 2004; **119:** 1027]. In contrast, rodents have higher rates of protein evolution for only 2 developmental and 1 physiological genes—these three genes being different from the 24 primate genes.

Patient at death's door---Drs. manage to pull him through.

Gene-Environment Tidbits of Interest

Aug 2004 Smoke, derived from burning plant material, has been known for some years to increase germination of a wide range of plant species**;** obviously, for plants to repopulate a region after a forest fire would be advantageous to us all. Now, **a specific compound** (derived from plant- and cellulose-derived smoke) **that stimulates germination** has been isolated and identified**:** butenolide 3-methyl-2*H*-furo[2,3-*c*]pyran-2-one [*Science* 2004; **305:** 977].

Performing a large insertional mutagenesis screen in **zebrafish**, the data [*PNAS* 2004; **101:** 12792] suggest there are ~1400 **embryonic-essential genes;** this report shows that 315 mutants (one-fifth of this total) have been cloned and identified. This mutant selection should become a valuable resource.

Whereas the number of environmental stressors on the planet runs into the millions, and the combinations of stressors run into even higher numbers, it is likely that all stressors elicit their toxic or carcinogenic effects via **a finite number** (*e.g.* 2 dozen or less) of modes-of-action [*Toxicology* 2002; **181-182:** 131]. A 69-gene set has been chosen to separate the maximal number of compounds into control, macrophage activator, peroxisomal proliferator, and oxidative stress/reactive metabolite classes *[Biochem Pharmacol* 2004; **68:** 2249].

Three genes are known to harbor **mutations that lead to cleft lip or palate** (**CLP**)**:** *HOX7*, *FGFR1*, and *IRF6* (the latter being interferon-regulatory factor-6). Possible teratogens for CLP include maternal smoking, dioxin, benzodiazepines, and perhaps phenytoin**;** "environment" must be a factor, since identical twins are not always concordant for CLP, *i.e.* both twins might not have the disorder. In a family-based association study, it was found that the Val274Ile mutation in the *IRF6* gene—when the child received one copy of this mutation from both parents—increases the risk of CLP to 9%, several times higher than that in the general population *[N Engl J Med* 2004; **351:** 769]. This represents an important advance in genetic medicine.

Sept 2004 **Arsenic-contaminated well water** in Bangladesh was associated with decreased intellectual function, in a dose-response fashion. Children with exposure levels above 50 µg/L had significantly lower scores than children with exposures below 5.5 µg/L [*Environ Health Perspect* 2004; **112:** 1329].

Genetic diseases need not be inherited via the germ line**; somatic mutations** can arise in discrete cell lineages early in embryonic development or during postnatal life. For the latter we think of cancer, but this mechanism also appears to occur with the autoimmune lymphoproliferative syndrome, **ALPS** [*N Engl J Med* 2004; **351:** 1409 & 1388].

Inflammation is a major means by which our bodies fight pathogens (virus, bacteria, fungus) and, if something goes awry, the result can lead to problems such as arthritis, Alzheimer disease, multiple sclerosis or heart disease. Chronic inflammation at a particular site can also lead to cancer. Now it appears that **NFκB is a key player**, because it might activate signaling pathways in both cancer cells and tumor-associated inflammatory cells—leading to malignancy [*Nature* 2004; **431:** 461 & 405].

Oct 2004 If you start a long-distance run with a sprint, within seconds your **hypoxia-inducible factor-α (*HIFA*) gene** triggers the glycolytic pathway to produce more ATP that is needed. *Hifa(-/-)* knockout mice were created, and they were able to swim faster and run uphill longer than normal mice—but at a price**:** by the final day of a 4-day exercise regimen, their muscles were clearly irreversibly damaged *[PloS Biol* 2004; **2:** e315]. Therefore, disrupting this gene might give you the gold medal, but at a serious price.

CYP3A4 and CYP3A5 are important enzymes that metabolize >50% of all prescribed drugs. Intriguingly, the frequency of the *CYP3A5*3* allele is significantly correlated with distance from the equator [*Am J Hum Genet* 2004; **75:** 1059]**;** the Met235Thr mutation of *AGT* [angiotensinogen (serine or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase; antitrypsin), member 8], an unlinked gene, shows a similar distribution—suggesting that **both of these *CYP3A5* and *AGT* alleles** may have resulted from the same selective pressure (of heat, correlated with latitude) and perhaps are associated with **salt sensitivity**.

Dec 2003 In phagocytosing cells (*e.g.* macrophages, neutrophils) the reactive oxygen species (**ROS**) precursor, superoxide, is produced by a

NADPH-oxidase complex. These oxidases are now designated **the *Nox* gene family** and are currently under intense investigation [*J Biol Chem* 2004; **279:** 51715].

Cadmium, a known human lung carcinogen, inhibits **DNA mismatch repair** (**MMR**). There are at least five *MSH* genes (*E. coli mutS* homologs) in the human genome. The MSH2-MSH3 and MSH2-MSH6 heterodimers (two different transcription factor proteins that bind together) are the specific targets for cadmium-induced inhibition of MMR [*J Biol Chem* 2004; **279:** 53903].

"Multiple Chemical Sensitivities Syndrome" (MCSS): What Is It, and What Is Known about It?

I am writing on behalf of Omnigraphics, a publisher in Detroit, to request your permission to reprint [the leading article from your] "***Interface*:Genes and the Environment**," University of Cincinnati Center for Environmental Genetics Fall/Winter 2001", in our upcoming reference book, Immune Systems Disorders Sourcebook, 2nd Edition.

Omnigraphics is a publisher that focuses on the limited area of producing reference volumes for public, school/college, and hospital libraries. Immune Systems Disorders Sourcebook, 2nd Edition, part of our Health Reference Series, will be a 500-600 page, edited, anthology-type book compiling reprinted material from public and private groups on topics related to genetic disorders for a lay audience. Each reprinted item will be accompanied by an appropriate credit citation listing the source of the material, and indicating that it is copyrighted and reprinted with permission. The purpose of our Health Reference Series is to serve the needs of libraries that seek printed compilations of reference material for patrons who wish to research personal health issues. As sourcebooks, our volumes also show consumers the types of information that is available from various organizations.

Permission was given!

Observations by a Biologist

How Many Genes Involved in Spore Formation?

The bacterium, *Bacillus subtilis*, can form two different cell types**:** a resistant spore, and a mother cell that can engulf the spore and surround it with a protective coat. How does this cell make everything happen on time? Moreover, how does the cell prevent everything from happening all at once?

During the 5-hour time period of "mother-child development", Locke and coworkers determined that 383 individual genes (representing 9% of the entire genome of 4,106 genes) are activated. The initiator of the entire process is sigma-E, which binds to RNA polymerase and increases its affinity (and therefore its ability) to activate a specific set of 262 genes. So, one set of genes turns on a 2nd set of genes (after which most of the 1st set gets turned off), which turns on a 3rd set of genes (after which most of the 2nd set gets turned off), and so on, and so forth [*PLoS Biol* 2004; **2:** e359].

This is a very simple example of "*systems biology*", or gene-gene interactions, which happens during the development (or generation) of different cell types.

Life is the art of drawing sufficient conclusions from insufficient premises.

Samuel Butler (1612-1680)

LETTERS TO THE EDITOR

RESPONSES/COMMENTS TO VARIOUS QUESTIONS

Q My 11-year-old daughter is taking a selective serotonin reuptake inhibitor (SSRI) for mental depression. I've heard comments both ways: is this a good thing or not?

A *It is the old story that perhaps began with birth control pills in the early 1960s. "If 10,000 women each take an oral contraceptive for 1 month and no adverse effects are reported, does this mean that the drug is safe for 100 women each to take these pills for 100 months?" Before 1980 essentially no children received antipsychotic drugs — because they had not been "proven to be safe" in children. Many believe that children's brains are still developing, until the age of 18 or even older. Various studies have shown a 3- to 10-fold rise in the use of antidepressants among children between 1987 and 1996, and an additional spike of 50 percent between 1998 and 2002. This dilemma is being revisited this year [Nature 2004;* ***430****: 401] and the final answers are not in yet. If a child is suicidal, might the drug help? Or might it make matters worse? Obviously, for the sake of your child's brain, it is always best not to expose her to unnecessary drugs. But — the bottom line is — when you believe the possible benefit of the drug outweighs the dangerous risks without the drug, then perhaps it's best to take the drug. Interestingly, advisors to the US Food and Drug Administration (FDA) have now recommended that all antidepressants include a warning that "these drugs cause some children to attempt suicide" [Nature 2004;* ***431****: 393].*

COMMENT The cofactor nicotinamide adenine dinucleotide (NAD) has just been elevated in its importance (to critical life processes) by work in yeast from the Milbrandt laboratory [*Science* 2004; 305: 1010 & 954]. NAD provides an important link between metabolism, cellular resistance to stress or injury, and longevity.

COMMENT The cipher laws related to the algorithms of Shor and of Grover have been used as encryption codes, where, for example, one letter of the alphabet is substituted for another. The first published "polyalphabetic cipher" was invented by Leon Battista Alberti (~1467), using a Caesar cipher to encrypt a message; knowing the code, his friend could decode the message.

The worm *C. elegans* begins development with exactly 1,090 cells, of which exactly 131 undergo programmed cell death (PCD) to result in the adult, which always comprises exactly 959 cells. During embryogenesis, exactly 113 undergo PCD — subdivided as 98 for the AB lineage, 14 for the MS lineage and 1 for the C lineage. The count of these cells undergoing PCD has been shown to comply with these cipher laws [*BBRC* 2004; 321: 515]..!

Q Some say that activated cancer genes (oncogenes), or inhibition of tumor suppressor genes, cause instability of the chromosomes, while others say that "chromosomal instability" causes cancer. Which one is correct?

A *Probably both are correct. The work of Vogelstein and others (on colon cancer more than a decade ago) certainly proved that, as more and more abnormal genes became activated during the process of "tumor progression", genomic instability clearly was one of the events that occurred ... eventually. This is most likely the more common scenario in cancer.*

In five families in which a child had a particular childhood cancer, receiving two copies (one from each parent) of an abnormally mutated BUB1B gene ("budding uninhibited by benzimidazoles-1-homolog-beta" in yeast) were discovered [Nat Genet 2004; ***36****: 1159]. This gene guides the cell's chromosome-partitioning system, and this might represent an example in which aneuploidy (abnormal numbers of chromosomes) occurs first, which then leads to cancer.*

CEG Members in the News

Dan Nebert was invited as Feature Speaker at the 20th Annual Meeting of the Mountain States Regional Genetics Network, sponsored by the American Board of Medical Genetics (Jul 04), Denver, Colorado**;** the reason for this invitation was his review article, "What does pharmacogenetics mean to the practicing physician?" [*Clin Genet* 1999; **56:** 247-258), which is used as reference material for the Annual Boards for the American Association of Medical Geneticists. **Dan** was also an Invited Speaker at the 3rd Annual Symposium on Pharmacogenomics, 2nd International "Biologie Perspective" Santorini Conference (Sep 04), Santorini, Greece.

Glenn Talaska was an Invited Participant at the Biological Monitoring portion of the International Health Sciences Institute (**ILSI**) Meeting, Research Triangle Park (Sept 04). **Glenn** also presented an invited seminar, titled ***"Molecular epidemiology: tools and methods for occupational and public health"*** at the School of Public Health, Ohio State University (Dec 04).

Nancy Warren gave a talk titled ***"Changing the face of the genetic counseling profession"***, Hueston Woods Conference Center, Dayton, OH, (Aug 04). She also delivered talks on ***"Starting a genetic counseling program at YOUR institution"***, at the National Society of Genetic Counselors Annual Education Meeting, Washington, DC (Oct 04), the American Society of Human Genetics Meeting, Toronto, Canada (Oct 04), and the Hispanic Congress of Health-Related Professions, San Juan, Puerto Rico (Dec 04).

SOME CEG MEMBERS ARE ALSO PARTICIPATING IN THE CINCINNATI BREAST CANCER & THE ENVIRONMENT RESEARCH CENTER (BCERC), co-funded by the NIEHS and the NCI. These include Center Director **Sue Heffelfinger** (Dept of Pathology); Deputy Director **Bob Bornschein;** Community Outreach and Translation Core (**COTC**) Director **Katie Brown;** and Center members **Ranjan Deka, Joyce Martin, Mario Medvedovic, Susan Pinney, Glenn Talaska, Craig Tomlinson** and **Dave Warshawsky** (all in the Department of Environmental Health).

In collaboration with three other Centers based at the University of California-San Francisco, Fox Chase Cancer Center (Philadelphia), and Michigan State University, the Cincinnati **BCERC** is working to**:**

- better understand the development of the mammary gland and how/when it is affected by environmental agents, by way of laboratory studies;
- learn more about how environmental and genetic factors affect the start of puberty in girls, by way of clinical studies (early puberty is a known risk factor for breast cancer later in life); and
- involve the community in the **BCERC**'s efforts to educate the public and policy makers about breast cancer research findings.

The first annual meeting of the four Centers participating in this 7-year project was held Nov 04 in Princeton, NJ. The Cincinnati Center was well-represented by six community breast cancer advocates, eight scientists, and two staff members. **Sue Heffelfinger** co-chaired a session on environmental carcinogenesis, as well as the poster session. **Bob Bornschein** served as a mentor for breast cancer advocates, attending an educational preview of the scientific topics to be presented at the conference. **Glenn Talaska** presented in a mini-Symposium on "***How carcinogens are evaluated and defined at an agency level***", and served as a panelist for a "***Talk with the experts***" session for breast cancer advocates. **Dave Warshawsky** presented a poster on "***Rat mammary organoids: metabolism and DNA binding of PAHs***". The Cincinnati **COTC**, led by **Katie Brown** and advocate Kathy Ball, took first place in the advocacy poster contest for "***Trading spaces: breast cancer advocates & researchers build a partnership***", based on the theme of the popular television program. The **BCERC** is now working to develop new collaborations so as to expand research on "breast cancer and the environment" at the University of Cincinnati.

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web-cytes

Although history books usually cater to presidents, kings, queens and military officers who have helped to shape the course of human events—**insects and other arthropods** have also done their bit. The URL http://scarab.msu.montana.edu/historybug is an interesting site with some fascinating stories about bug-borne diseases, how historical events have been changed due to "these bugs", and other interesting tidbits about such insects and parasites.

Do you find yourself saying that you can predict the weather at least 50% of the time, while that guy (or girl) on TV seems to be missing it at least 75% of the time? If you want to become even a better expert on **meteorology**, check out www.meted.ucar.edu **.** This site lets you delve into more than 100 topics, from the southern Pacific Ocean's El Nino Oscillation cycle, to dust-storms, and hurricane predictions.

A unique genome-wide and nonredundant **mouse transcription factor database**, and its viewer http://genome.gsc.riken.jp/TFdb/**,** has been developed by the Genome Science Laboratory of RIKEN in Japan. This URL should provide useful information for systematic genome-wide studies of transcriptional regulation [*BBRC* 2004; **322:** 787].

Here is a website to help researchers quickly find **fruit fly** (*Drosophila melanogaster*) **genes** that have orthologs (equivalent genes) for human diseases http://superfly.ucsd.edu/homophila **.**

Bioinformatics expert Bertram Weiss of Schering AG (Berlin) offers a compendium of information on **genes and their effects** from WormBase, FlyBase, Online Mendelian Inheritance in Man (OMIM), and other collections www.phenomicDB.de **.** This site allows the visitor to understand which genes cause different traits (phenotypes) across various species.

For more than 1200 human (and mouse) proteins that function **in the cell's nucleus**, check out http://npd.hgu.mrc.ac.uk/index.html , and for dozens of movies about things happening inside the cell's nucleus, check out www.cellnucleus.com **.**

Don't worry about what people "think"
..... they Don't Do it very often ***(source unknown)***

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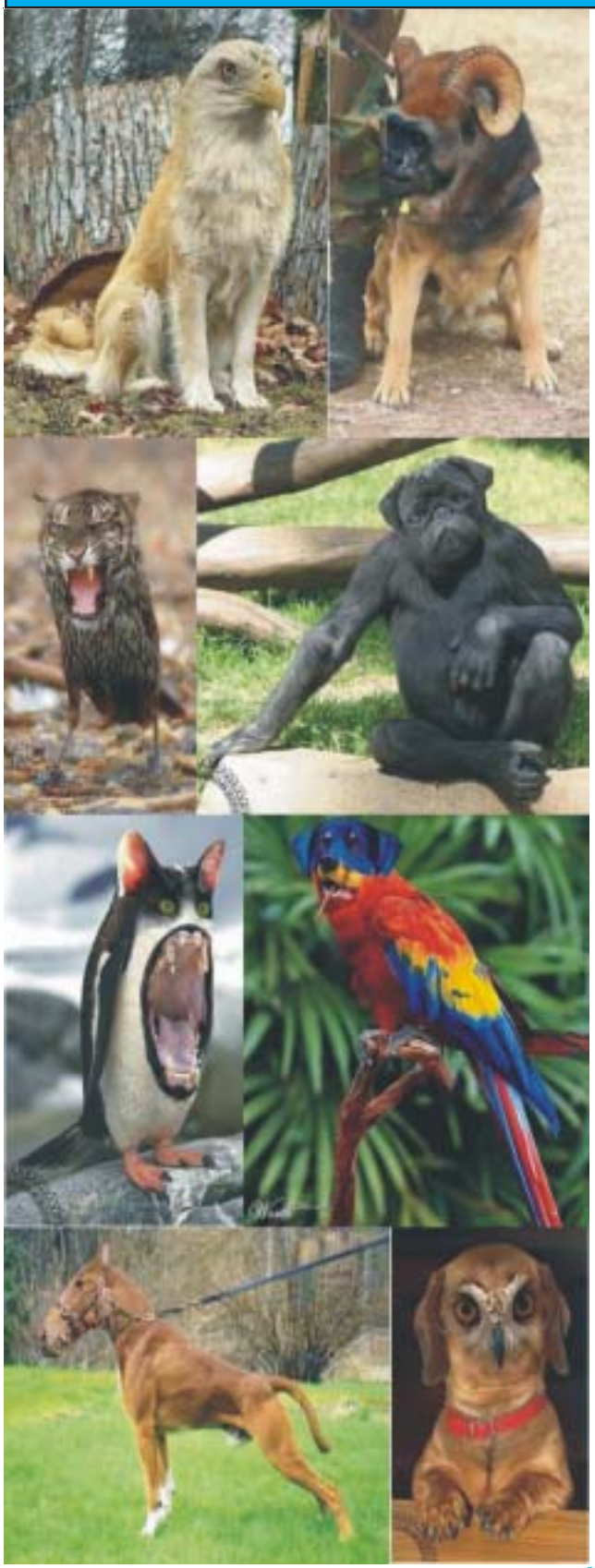

New Species?

RETREAGLE
DOGIBBORAM
HAWKAT
PUGORILLA
CATQUIN
MACAWNINE
BOXORSE
DOXOWL

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Graduate students say the darndest things

KUPPER CELLS=Kupffer cells
SPEEN= SPINE
PSORASIS=PSORIASIS
MICROPHAGES=macrophages
SUMPTIVE=? consumptive
SYNTHETIZED=synthesized
β-ACTION=β-ACTIN

When the only tool you own is a hammer, every problem begins to look like a nail.

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

Tidbits from the last half of 2004**:**

Jul 2004 **The entire *UGT1A1* gene** (enhancer, promoter, all 5 exons and their flanking regions) was resequenced in 195 Japanese subjects [*Clin Pharmacol Ther* 2004; **75:** 501; 495]. This elegant, complete study revealed two linkage disequilibrium (**LD**) blocks separated by a recombination "hot spot", dividing exons 1 from exons 2-5. Four and two haplotype groups were assigned to LD blocks 1 and 2, respectively. Even more excitingly, a particular haplotype was associated with those patients who developed high bilirubin levels (early indicator of liver damage) after receiving **irinotecan** (as treatment for cancer).

More and more diversity within the genome continues to be appreciated. **Large-scale copy number polymorphisms** (**CNPs**) represent large duplications and deletions of usually 100 kb to more than 2 Mb**;** these seem to occur, on average, at a frequency of ~11 per human individual tested [*Science* 2004; **305:** 525]. These CNPs will affect an individual's ability to respond to a drug or environmental chemical and override specific SNPs—causing an (unwanted) **equivocal genotype**.

Aug 2004 It is recommended that, when possible, these CNPs (also called **large-scale variations**, **LCVs**, and multisite variants, **MSVs**) "be avoided when looking at markers for genotype-phenotype association studies" [*Nat Genet* 2004; **36:** 789]. Hmm. But—how do we **know ... when** to avoid these large-scale duplications or deletions?

These **duplicons** comprise at least 5% of the genome and many are yet to be annotated in the human genome draft [*Nat Genet* 2004; **36:** 861].

Nonsense-mediated decay (**NMD**) is the recognition of premature termination codons, leading to degraded messenger RNA [*Nat Genet* 2004; **36:** 801]. Here is yet-another mechanism by which genomic diversity can lead to an equivocal genotype**..!**

Variation in the **baseline expression level** of many genes has a heritable component. Examining 3,554 genes in 14 large gene families by microarray analysis [*Nature* 2004; **430:** 743 & 733], almost one-third showed linkage of expression phenotypes to specific chromosomal regions—lending further credence to the complexity of the genome. Many unlinked genes may share the same (*trans*)-regulatory signal**..!**

There was a report [*Nat Genet* 2003; **35:** 171] that variation in the *XBP1* gene contributes to susceptibility to **bipolar affective disorder**. Another group has now refuted this study [*Nat Genet* 2004; **36:** 783]. This is another example of a genotype-phenotype association study in which "now-you-see-it-now-you-don't" (**NYSINYD**). Possible explanations to explain the discrepancies between the two studies include [a] incorrect diagnosis (*i.e.* equivocal phenotype) and [b] different ethnic alleles or other genomic variations (*i.e.* equivocal genotype).

Sep 2004 Three genes in the **glutathione *S*-transferase** gene superfamily (*GSTM1, GSTP1, GSTT1*) were studied for risk of allergic asthma in 246 Danish families, using the family-based transmission disequilibrium test (**TDT**). The *GSTM1* and *GSTT1* genes have "null" allele frequencies between 20% and 50% in various ethnic populations. Absence of the *GSTM1*0* allele (P <0.00005) and of the *GSTT1*0* allele (P = 0.021) were determined to be risk factors for **atopic asthma** [*Hum Mutat* 2004; **24:** 208].

DNA segments of 500-1,000 bp, spaced at intervals of 1-2 Mb across the genome, complete with established locations of SNPs, provide **linkage information** that equals or exceeds that of traditional marker-based approaches [*Am J Hum Genet* 2004; **75**: 647].

To discover genes that contribute to complex traits, **admixture mapping** has been suggested to be helpful. Using samples from recently admixed populations, one might detect susceptibility loci at which the risk alleles have different frequencies from that in the original contributing populations. New statistical methods to detect "ancestry association" are described and available on the web [*Am J Hum*

Genet 2004; **75:** 771].

As we reported in the last ***Interface*** issue, successful gefitinib treatment of **non-small-cell lung cancer** is associated with a mutation in the tyrosine kinase domain of the *EGFR* gene [*N Engl J Med* 2004; **350:** 2129; *Science* 2004; **304:** 1497], but the association is not 100%. Now come further letters-to-the-editor, supporting this contention [*N Engl J Med* **351:** 1260]. Ho-hum. Such is the problem with all genotype-phenotype association studies**..!**

Oct 2004 **Curcumin** (derived from the curry spice, turmeric) inhibits a calcium pump (sarcoplasmic reticulum Ca-ATPase) and has a low degree of toxicity. The **ΔF508 mutation of the cystic fibrosis CFTR protein** is known to be "misprocessed" in the endoplasmic reticulum**;** this results in the CFTR protein, getting abnormally degraded as soon as it is made, and the final outcome is bacterial invasion and inflammation (as part of the CF disease). Curcumin was therefore used to treat CF mice, and it worked [*Science* 2004; **304:** 600]**..!** No doubt clinical trials are now underway. Here is a pharmacogenetic example of a specific drug—chosen because it is known to attack a specific target.

The **ENCyclopedia Of DNA Elements** (**ENCODE**) **Project** has begun to face the enormous task of interpreting the human genome and learning how to use this information to understand the biology of all human health and disease [*Science* 2004; **306:** 636]. The pilot phase is to focus on one 30-Mb region**;** an international consortium of computational and laboratory-based scientists is working on this region to detect all sequence elements that confer biological function, comparing the genomes of 26 mammals.

The **melanocortin-1 receptor** (*MC1R*) gene has more than 65 alleles with amino-acid changes, and this one gene accounts for the wide gradient (across the entire planet) of skin and hair color, sun sensitivity, and incidence of skin cancer [*Am J Hum Genet* 2004; **75:** 739].

The first phase of the **Environmental Genome Project** (**EGP**) is now complete [*Genome Res* 2004; **14:** 1821]**; 213 genes** involved in DNA repair, metabolism, cell-cycle regulation and apoptosis were resequenced (a "substantial amount" of introns, all exons, 1.3 kb upstream and 1.3 kb downstream) in 90 subjects of different ethnic backgrounds. Phase II of the EGP will do the same for an additional 350 genes, as well as explore any biological relevance and functional significance of the 23,443 SNPs identified in phase I.

Nov 2004 An increased risk in **the metabolic syndrome** (hypertension, high cholesterol, low magnesium) is associated with a mutation in a mitochondrial gene [*Science* 2004; **306:** 1190], underscoring that fact that we must consider the mitochondrial, as well as the nuclear, genome—when one studies complex diseases.

In members of 6 families with many individuals affected by **autosomal dominant late-onset Parkinson disease** (and other neurodegenerative disorders such as Alzheimer disease and Lou Gehrig disease), mutations in the *LRRK2* (leucine-rich-repeat kinase-2) gene at Chr 12q12 have been found [*Neuron* 2004; **44:** 601]. This group had previously narrowed a cause for this disease to a region of chromosome 12 and called it "PARK8".

Some patients with severe rheumatoid arthritis or polymyositis are treated with **methotrexate** (a cancer drug). Now, it has been shown [*J Natl Cancer Inst* 2004; **96:** 1691] that it is possible (although rare) to "reactivate" a dormant Epstein-Barr virus (**EBV**) in some people—which can be responsible for **causing lymphoma**.

Dec 2004 **RNA editing** (usually changing adenosine to inosine) can lead to the posttranscriptional creation, or elimination, of splice signals—affecting alternatively spliced Alu-derived exons [*PLoS Biol* 2004; **2:** e391]. This phenomenon has significant implications for cellular gene expression and problems with attaining an **unequivocal genotype** in clinical genotype-phenotype association studies.

Contrary to considerable success in treating non-small-cell lung cancer with gefitinib due to mutations in the *EGFR* gene of these tumors, somatic mutations in the *EGFR* gene in **colorectal cancers and glioblastomas** are present at very low rates—

indicating **gefitinib therapy is unlikely to improve** patients having these types of cancers [*N Engl J Med* 2004; **351:** 2883].

Comparing all 2,756 patients diagnosed with **lung cancer** within the Icelandic population—from 1955 to 2002—with an extensive genealogical database containing all living Icelanders, and most of their ancestors since the initial settlement of Iceland in 874 A.D. [*J Am Med Assn* 2004; **292:** 2977], it was concluded that **tobacco smoke** plays a dominant role in the pathogenesis of this disease, even among those individuals who are **genetically susceptible** to lung cancer.

Genaissance Pharmaceuticals (New Haven CT) announced that they "had discovered genetic markers that the Company believes will predict who is at risk of developing **clozapine-induced agranulocytosis**" (a life-threatening decrease of white blood cells), but they were "not at liberty to say what these markers are".

Loss of *PTEN* gene function in **prostate cancer** is highly correlated with activation of *AKT*, and this, in turn, is associated with the phosphorylation of "S6", one of its main effectors. Antibodies to these three gene products are potentially able to define a molecular signature of *PTEN* loss and/or *AKT* pathway activation and determine which patients might have a prostate cancer treatable by one of these regimens *[Clin Cancer Res* 2004; **10:** 8351].

After rejecting the **AmpliChip Cytochrome P450 Genotyping Test** (manufactured by Roche Molecular Systems, Inc., Pleasanton, CA**;** using the Affymetrix GeneChip MicroArray Instrumentation System) in Nov 03, the **FDA has now approved** this test as the "first laboratory test system for doctors to use in reviewing patients' genetic information, before prescribing certain classes of drugs". The caveats and problems in relying upon this genetic test, however, have recently been reviewed in detail *[Eur J Pharmacol* 2004; **500:** 267].

Genetic Variation and Geographically--Isolated Subgroups, across the Planet

There is an entire supplemental issue (Nov 04) of *Nature Genetics*, devoted to the genetic implications of "race", which encompasses ethnic groups as well as major geographically-isolated subgroups of human populations. If an isolated population has interbred only among themselves for 10,000 years or more, without any interference from outside people, this is the definition of a truly "geographically-isolated subgroup". Examples include**:** Africans, East Asians, Caucasians, Oceanians from the south Pacific, and Amerindians.

In one article, **forensic genetics** is examined [*Nat Genet* 2004; **36:** 58] in which it is argued that all geneticists should anticipate the ethical and social issues associated with nonmedical applications of genetic variation research. Within this overview, a fascinating table is included [from *Forensic Sci Int* 2001; **119:** 17] where a set of 10,000 profiles in the United Kingdom was simulated from each of five ethnic groups (Caucasian, Afro-Caribbean, Indian subcontinent, Southeast Asian, and Middle Eastern)**;** British police officers were asked to designate ethnicity based on appearance (plus criminal records taken when individuals were arrested for a crime) rather than any knowledge of an individual's ancestry.

Correct predictions by the policemen occurred 56% of the time for Caucasians, 67% for Afro-Caribbeans, 43% for those of the Indian subcontinent, 66% for Southeast Asians, and only 30% for Middle Easterners.

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"Q"uote of the Month

The saddest aspect of life right now is that science gathers knowledge faster than society gathers wisdom.

Book of Science and Nature Quotations*, 1988.....*Isaac Asimov 1920-1992