

INTERFACE:

GENES AND THE ENVIRONMENT

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Transgenic "See-through" Fish as a Sentinel for Water Pollution

Chromosomes are composed of the genetic material, deoxyribonucleic acid (DNA), and are located in the nucleus of every replicating cell. The DNA is arranged in a linear string of genes. Soon we will know the total number of human genes on all 23 chromosome pairs comprising the genome for *Homo sapiens*; the current estimates for the number of genes run between 30,000 and 45,000. The nematode (roundworm) *Caenorhabditis elegans* has a genome of ~19,100 genes. The fruit fly *Drosophila melanogaster* has a genome of about 13,600 genes. The tiny mustard plant *Arabidopsis thaliana* has a genome of about 26,000 genes.

Signals (such as those produced by chemical and physical agents) are "received" by receptors on the

cell surface or within the cell's *cytoplasm*, and a "signal transduction cascade" sends these signals to the cell *nucleus*, activating genes to express a response.

Environmental Signals Detected by Reporter Genes

During such *gene activation*, DNA is transcribed into various forms of RNA in the nucleus and nucleolus, the transcripts are spliced to form messenger RNA (*mRNA*), most of which is delivered through the nuclear pores to the cytoplasm, where after further modification it is then translated to *protein*. Examples of proteins include *globin* (from which hemoglobin is made), green fluorescent protein (**GFP**, a fluorescent protein found in the jellyfish), and *luciferase* (**LUC**), the enzyme responsible for a firefly to glow). The *GFP* and *LUC* genes are called *reporter genes*, because they are able to "report" the response of a signal. They are especially valuable in vertebrate cells, because these genes (from jellyfish, firefly) are not normally present in cells of vertebrates (human, mouse, fish). Recently, additional reporter genes (causing a red, blue or yellow color) from bacteria have also been characterized.

In the cell there is machinery that drives, or turns on, each gene during gene activation. The machinery includes *receptor* and *transcriptional proteins* that recognize the above-mentioned signals and then bind to *enhancer regions* (sometimes far upstream or downstream from the gene on the DNA strand), and other proteins that bind to *promoter regions* (very close to that part of the gene which will be transcribed into RNA).

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Enhancers Important to Environmental Toxicants

In the past 20 years, a number of enhancer regions (DNA motifs) have been characterized in dozens of labs. These include the metal response element (**MRE**), the aromatic hydrocarbon response element (**AHRE**), the estrogen response element (**ERE**), the electrophile response element (**EPRE**), and two retinoic acid response elements (**RARE**, **RXRE**). Heavy metals such as *cadmium*, *zinc* or *mercury* turn on particular genes via the MRE. *Dioxins*, polychlorinated biphenyls (**PCBs**), and *benzpyrene* generated in combustion processes (and present in oil slicks) turn on other genes via the AHRE. Environmental and natural *estrogens*—including *endocrine disruptors*—turn on specific genes via the ERE. *Oxidants* such as some heavy metals, bleaching agents and *hydrogen peroxide* turn on distinct genes via the EPRE. Certain *retinoids*, some of which can cause birth defects, turn on still other genes via the RARE and RXRE.

Bioconcentration in Fish

A famous experiment by B.B. Brodie in the 1950s dramatically showed the principle of “bioconcentration” in goldfish. Several fish were placed in bowls of 1,000 ml, 400 ml, and 100 ml of water each containing 10 millimolar chlorpromazine (a tranquilizer) [“10 millimolar” means about 6000 billion billion molecules per liter]. This means the first fish were “exposed” to **6000 billion billion**, the second fish exposed to **2400 billion billion**, and the third fish exposed to **600 billion billion** molecules of chlorpromazine. Because of *bioconcentration* (the more chemical in the water available to the animal, the more is transferred into that animal), the first fish were *comatose*, the second fish were *dizzy* but not comatose, and the third fish were swimming *happily*. Environmental chemicals are likewise bioconcentrated in all fish to varying degrees: *e.g.* dioxin in the water has been shown to be concentrated **~10,000 times** inside the fish!

Designer Fish

All of this knowledge was applied at the University of Cincinnati Medical Center, between 1994 and 1999, into building transgenic zebrafish (a small guppy-sized fish originally recovered from rivers of Northern India). Because the genome of the zebrafish is small, it will be the first fish to have

its genome completely sequenced (within the next 1-2 years). Constructs such as **AHRE-GFP** and **MRE-LUC**, for example, were generated by Michael Carvan in the Nebert laboratory and have been injected into fertilized zebrafish eggs. This means that the embryonic or adult fish will contain one of these reporter genes in virtually every cell of its body. When such a transgenic zebrafish is exposed to, for example, **PCBs** or **cadmium**, respectively, this environmental “signal” in the fish tank will cause the reporter gene to be activated. Detection systems—such as a fluorescence light microscope for **GFP** expression (**Figure 1**) or a luminometer for **LUC** expression—will then determine the concentration of environmental pollutant in the water in which the zebrafish was swimming (the higher the levels of pollutant, the higher the expression of the reporter gene). Fish with little or no skin pigment are

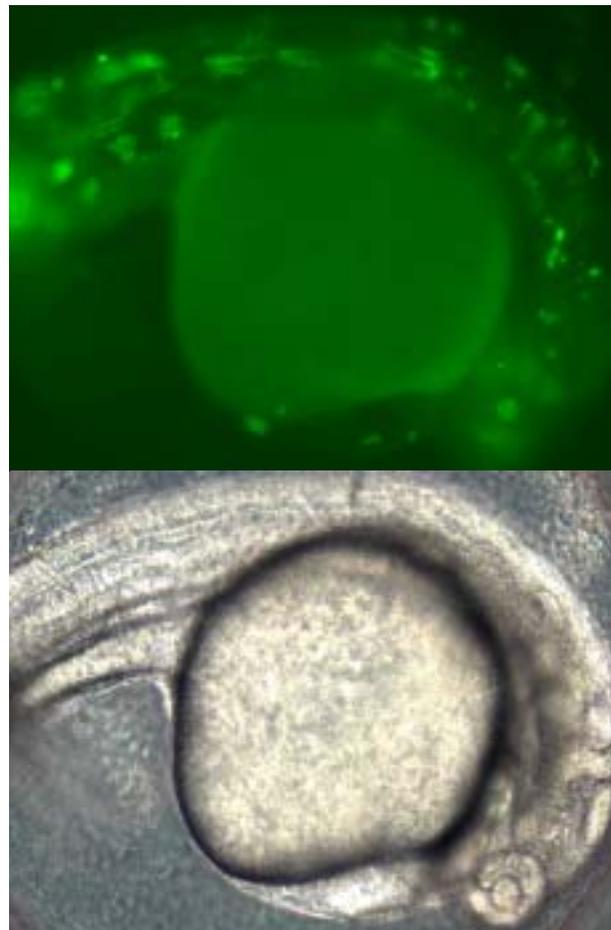


Fig. 1. Fluorescent microscopy of 3-day-old zebrafish “fry” (upper panel) and phase contrast photo of same field (lower panel). Note GFP signaling comes not from the large circular yolk sac but from the fish embryo that is curled around the yolk sac. The eye is at lower right.

being used, because pigment on the skin can interfere with quantitation of the reporter gene. If the detection system does not kill or injure the fish, it is also possible for the fish to “detox” itself over the next several days or weeks and be used again—for as long as the zebrafish lives (which is 2 to 3 years).

Conclusions and Looking to the Future

More than 80,000 different *pesticides*, *fertilizers* and *herbicides* each year are being poured on America’s farmlands, pastures and lawns. Hundreds of *toxic waste dump sites* (containing sealed barrels of PCBs, heavy metals, etc.) have been identified in the United States, with the possibility that these buried large containers of dangerous chemicals will eventually rust and the pollutants will leach into the groundwater. All fish in nearby streams, lakes or bays will be exposed to, and will bioconcentrate, these chemicals. Humans, at the end of the food chain, will suffer the consequences of such *aquatic pollution*, by drinking contaminated water and, especially, if they eat a lot of contaminated fish. For example, there are reports of lower I.Q. tests in children born of mothers who live in the Great Lakes Region and have consumed large amounts of contaminated fish during their pregnancies.

A company is being set up for the development of these above-described *transgenic fish*, which will offer unique opportunities for a simple, quick, exquisitely sensitive, and inexpensive assay for monitoring aquatic pollution. This research is an example of how our growing knowledge of molecular biology and genetics can be combined with “real-life” problems, such as a contaminated water supply and its possible *impact on human health*.

Placing these fish in creeks near toxic waste dump sites where there is the potential for nasty pollutants to leach into a nearby creek, and ultimately into drinking water supplies, for example, would be similar to using canaries to monitor for noxious gases in coal mines. In either case, this is a *sentinel for pollution*— alerting us to potential toxicity and thus is likely to prevent human exposures and subsequent environmental diseases.

—Contributed by Dan Nebert and Marian Miller.

{Described in *Environ Health Perspect* 2002; **110**: A15 & refs therein}

Latest in Genetics and Genomics....

What follows is a synopsis of some of the more interesting things that have happened during the first 6 months of 2003 with the Human Genome Project (HGP), and related genetics/genomics news, provided chronologically:

Jan 2003 The January 1st issue of *Nucleic Acids Res* represents a massive 516-page compendium of the most extensive listing to date of **biological databases**.

At a 2-day workshop in Florida, the topic of data-mining was discussed. Bioinformatics people accused the large genome sequencing centers of hoarding data, or trying to restrict use of the data, while the DNA sequencers alleged that bioinformaticists were stealing credit, “scooping” them before they could publish an analysis of their hard-earned data. It was agreed upon that large-scale sequencers must release their data—whatever the risks—and the users must be respectful of those who produced the data and *give credit where credit is due* [*Science* 2003; **299**: 487; *Nature* 2003; **421**: 877].

Many past issues of *Interface* have described *RNA interference (RNAi)*, a naturally-occurring mechanism for gene down-regulation in many organisms that works by tying up mRNA so that it cannot make a protein. Using RNAi, the worm community is systematically “knocking-down” each of 16,757 genes in the *Caenorhabditis elegans* genome, in order to see what effect the absence of each gene has on the animal’s overall phenotype (trait) [*Nature* 2003; **421**: 220, 231, 268].

Feb 2003 Also as described previously in *Interface*, from the Cancer Genome Anatomy Project (CGAP) laser-dissection gene-capture database, there are thousands of unidentified genes that are either up- or down-regulated during all types of cancer formation, as compared with genes expressed in normal tissues. Characterization of the human **breast cancer** and **salivary gland expression gene (BASE)**, for example, might help in the diagnosis or treatment of breast or prostate cancer [*PNAS* 2003; **100**: 1099].

Trying to “find” genes in the genome sequence is only as good as the software programs that have been designed for carrying out this task. By comparing the human and mouse genomes for areas of DNA sequence conservation, an estimated 1,019 additional genes have been discovered [*PNAS* 2003; **100**: 1140].

The finished sequence of human **chromosome 14** comprises 87,410,661 bases, having 1,050 identified genes and gene fragments and 393 pseudogenes representing 100% of its euchromatic region [*Nature* 2003; **421**: 601].

Mar 2003 Genes whose DNA is transcribed together in response to a signal represent a transcriptosome. Moving toward “systems biology,” comprehensive genetic screens of entire mouse, human and plant transcriptomes—by considering gene expression values as quantitative traits—are beginning to show us how many genes actually work together in concert, in response to a particular endogenous or exogenous signal [*Nature* 2003; **422**: 297].

Apr 2003 The Human Genome Project declared that the sequencing of the three billion bases of human DNA is complete, as of **April 14th**—the **50th anniversary** of the Watson-Crick discovery of the DNA helical structure.

A “vision for the future of genomic research,” by Francis Collins and colleagues [*Nature* 2003; **422**: 835; *Nat Genet* 2003; **34**: 1] suggested that the **Human Genome Project** is the foundation, that Genomics to Biology, to Health and to Society represent the three floors of the building, and that the structures holding these floors in place include Education, ELSI (ethical, legal and social issues), Training, Computational Biology, Technology Development, and Resources.

Leptospirosis is a waterborne infection in tropical and subtropical countries where sewage disposal is poor; symptoms include liver and kidney damage and bleeding from the lungs. The spirochaete pathogen *Leptospira interrogans* genome was sequenced in Shanghai [*Nature* 2003; **422**: 888] and predicted to have 4,768 protein-coding genes.

The genome of the filamentous fungus *Neurospora crassa* (the most commonly studied fungus in genetics research) has a ~40-megabase (Mb) genome encoding ~10,082 protein-coding genes [*Nature* 2003; **422**: 859]—only about 25% fewer than that in the fruit fly *Drosophila melanogaster*. *N. crassa* has developed a mechanism, called “repeat-induced point” mutation (RIP), whereby repeated genes and duplicated repetitive sequences are destroyed via mutation.

May 2003 The common theme (this year) continues: how many functional genes really exist in any of the sequenced genomes? Attempts to amplify and clone all predicted protein-coding open-reading frames (ORFs) for *C. elegans* is called the ORFeome Project [*Nat Genet* 2003; **34**: 8, 35] and shows that more than 50% of predicted genes require corrections in their intron-exon structures.

The finished sequence of human **chromosome 7** comprises 157,953,789 bases, having 1,917 protein-coding genes, more than 360 of which are disease-associated [*Science* 2003; **300**: 767]. They found 440 chromosome rearrangement breakpoints associated with disease.

By comparing baker’s yeast *Saccharomyces cerevisiae* with three related species (*S. paradoxus*, *S. mikatae*, *S. bayanus*), the Whitehead/MIT Center for Genome Research determined that about 15% of all original genes required corrections, and the total number of genes is decreased from ~6,000 to 5,538 [*Nature* 2003; **423**: 241].

The term “phenotype” is used to refer to any biochemical, physiological, morphological or behavioral characteristic of an organism. The PhenoFocus email chat group comprises many dozens of human geneticists, genomics scientists and clinicians who are working hard to quantitate clinical phenotypes (in mice and other lab animals, as well as humans). Nelson Freimer and Chiara Sabatti at UCLA, members of this chat group, have now proposed the establishment of an international Human Phenome Project (HPP), which would bring together a wide range of scientific disciplines—including clinical investigation, epidemiology, human and model-organism genetics, statistics, and informatics (*Nat Genet* 2003; **34**: 15). It is anticipated that we will hear a lot more about this during the coming months.

Jun 2003 A draft sequence of the completed chicken genome is expected next March [*Science* 2003; **300**: 1669]. To date, the species most closely related to mammals (human, mouse) having had their genomes sequenced is *Takifugu rubripes* (puffer fish)—with a common ancestor ~400 million years ago (MYA). Because birds and mammals shared a common ancestor ~300 MYA, knowledge about the chicken genome will bridge an important evolutionary gap.

Phylogenomics represents the intersection of evolution and genomics [*Science* 2003; **300**: 1706]. In earlier issues of *Interface*, we cautioned that “lateral, or horizontal, gene transfer” might confuse our knowledge about evolution; in fact, it appeared that the human genome might be “infected” with hundreds of bacterial genes [*Nature* 2001; **409**: 860]. This has been refuted [*Science* 2001; **293**: 1048; *Nature* 2001; **411**: 940, 1013], and whole-genome studies now suggest that lateral gene transfers have been rare over the course of evolution.

The finished sequence of 95% of the human **Y chromosome**, containing the male-specific region (MSY), contains 156 transcription units which include 78 protein-coding genes that collectively encode 27 distinct proteins [*Nature* 2003; **423**: 810, 825]. *Ampliconic regions* of >99.9% identity show how the unpaired Y chromosome can duplicate itself during cell division. *X-degenerate* and *X-transposed regions* give us a glimpse of the evolutionary strategies the Y chromosome has used to survive.

In early 2000, an informal contest began at the Cold Spring Harbor Laboratory genome meeting, in which scientists tried to guess just *how many*

protein-coding sequences would be in the human genome. With most guesses in the 80,000 to 200,000+ range, Lee Rowen (Seattle) was declared the winner with hers being the lowest of all estimates—25,947—which is closest to the *current reckoning of 24,847* made by the Ensemble genetic database. The final gene tally remains unknown but is unlikely to rise beyond 30,000 to 40,000 protein-coding sequences [*Nature* 2003; **423**: 576; *Science* 2003; **300**: 1484].

CEG Members in the News

Dan Nebert gave an invited lecture at the Conference on Molecular and Genetic Epidemiology and Cancer, co-sponsored by the American Association for Cancer Research (AACR) and the Society of Toxicology (SOT), Waikoloa, Hawaii (Jan 03). He was also an invited speaker at the Symposium on “Race and Ethnicity in Medical Scientific Research” during the Annual Meeting of the American Association for the Advancement of Science (AAAS), Denver, Colorado (Feb 03).

Glenn Talaska was invited to be a member of the International Advisory Committee for the Sixth International Symposium on Biological Monitoring in Occupational and Environmental Health, International Congress of Occupational Health, Heidelberg, Germany, in 2004. He also gave a presentation entitled, “*Carcinogen biomarkers following occupational and environmental exposures.*” and was a part of the Organizing Committee for the NIOSH-sponsored Meeting “Applying Biomarkers to Occupational Health Practice” (Apr 03).

Craig Tomlinson presented an invited lecture at the Plant and Animal Genome International Conference (San Diego, CA, Jan 03).

Nancy Steinberg Warren made presentations at the Genetic Counseling Program to the CCDD: Maternal and Child Health Site Visit (Feb 03), and at the Pedigrees workshop for the Genetics Summer Institute for National Nursing Faculty, CCHMC (Cincinnati, OH, Jun 03).

David Warshawsky presented a lecture entitled “*Potency of complex mixtures*” at the USEPA in Washington DC (Mar 03) and at the USEPA Region 5 workshop (Chicago, IL, Apr 03).

Diabetes Explosion in the U.S.

Given the current trend, a scientist at the Centers for Disease Control & Prevention (CDC) warned that *one of three U.S. children born in 2000 will become diabetic* unless this country gets serious about eating less and exercising more. Why is the prevalence of type-2 diabetes mellitus exploding in this country?

Type-1 diabetes is insulin-dependent and has an association with autoimmune disease (in which auto-antibodies destroy the pancreatic-islet beta cells) and perhaps also with viral infections. These patients are thin and prone to ketosis. **Type-2 diabetes** is non-insulin-dependent, *i.e.* altered insulin secretion and insulin resistance; these patients are overweight and the disease is brought on more quickly (at an earlier age) by obesity.

James V. Neel’s “thrifty gene” hypothesis [*Am J Hum Genet* 1962; **14**: 353] suggests that mutant advantageous alleles can “evolve” in response to selective pressures—for example, conditions of predictably alternating feast and famine that characterized the traditional human lifestyle, and which would lead to obesity and diabetes in the modern world where food is abundant all the time and exercise is avoided.

Jared Diamond [*Nature* 2003; **423**: 599] takes this one step further and offers an hypothesis as to why the U.S. is seeing this explosion in diabetes. The lowest prevalence (practically zero) of type-2 diabetes is in rural Third-World areas, whereas the highest (37-50%) is seen among Nauru Islanders of the tropical Pacific, Pima Indians in Arizona, and urban Wanigela people in Papua New Guinea. Each of the latter three populations have undergone a *sudden change* (in just 1-2 generations) from famine to a sedentary life with plentiful food. In contrast, Diamond suggests that Europe has undergone a *gradual change* (from less eating/more exercise to more eating/less exercise) between the 1400s and 1700s, whereas Blacks and Hispanics in the U.S. population have also undergone a sudden change. Diamond offers seven questions that can be asked, and predictions that can be tested by epidemiological studies in certain populations around the world—to corroborate or discard his intriguing theory!

“Q”
quote of the month

You only live once, but if you work it right, once is enough.....
Joe E. Lewis, 1902 - 1971.

Biotechnology....

Jan 2003 Although China has worked with fast-growing transgenic carp (having the growth hormone gene GH) and Cuba is considering commercialization of similarly fast-growing tilapia (a fresh water fish), approval in the U.S. for commercial farming of transgenic salmon is still at least 18 months away—mostly due to the Food & Drug Administration (FDA) lacking the expertise to evaluate environmental risks of such fish [*Nature* 2003; **421**: 304].

The enzyme α 1,3-galactosyltransferase (α 1,3Gal) makes the major antigen that causes rejection in pig-to-human organ transplantations. Pigs lacking the α 1,3Gal gene have been generated [*Science* 2003; **299**: 411], and thus should be safer for human use.

Feb 2003 Bisphenol A (BPA) is a known endocrine disrupter (disrupting normal hormonal physiology). In high doses, BPA temporarily activated aggressive behavior in mice; at low doses, BPA interfered with normal development of the reproductive organs [*Environ Health Perspect* 2003; **111**: 175, A110].

Agro-pharmaceutical companies reported that U.S. livestock farmers used fewer pounds of antibiotics in 2001, for the third straight year: 21.8 million, down from 24 million in 1999 [*Environ Health Perspect* 2003; **111**: A87].

Although the new maximal contaminant level for arsenic in drinking water is 10 parts per billion (ppb), the U.S. Environmental Protection Agency (EPA) estimates that ~350,000 people in the U.S. drink water containing more than 50 ppb. Arsenic activates the oxidative stress signaling pathways, is associated with TP53 mutations, and induces skin and urinary bladder cancer [*Cancer Causes Control* 2003; **14**: 303]. Arsenic poisoning in India is widespread [*Nature* 2003; **421**: 778].

Mar 2003 It is tempting to speculate that microRNAs, that abundant class of ~21 nucleotide-long nontranslating RNAs involved in RNAi in plants and animals, are important in specifying cell differentiation, developmental patterning, and cell death [*Science* 2003; **299**: 1540; *Cell* 2003 **113**: 25 & 673; *Curr Biol* 2003; **13**: 790]. There are between 1,500 and 2,000 of these miRNA genes in the human genome [*Genes Dev* 2003; **17**: 438].

A study of transgenic beets in Denmark showed that more weeds and insects survived after herbicide application, although beet yields were not diminished. One year positive results may be outweighed by longer-term drawbacks, however, because

weeds in glyphosate-treated sites are killed before they can produce seeds in late summer [*Nature* 2003; **422**: 250].

A federal judge ruled invalid the University of Rochester's sweeping claim to lucrative anti-inflammatory drugs, ruling that "the patent was little more than a research plan." The patent was filed in 1992 and finally won in 2000—years after several drug companies had already developed specific cyclooxygenase-2 inhibitors and earned billions of dollars selling them [*Science* 2003; **299**: 1638].

Manyazole compounds developed as inhibitors of fungus sterol 14 α -demethylase can also inhibit the mammalian enzyme CYP51A1 plus aromatase (CYP19A1), thereby qualifying these drugs as endocrine disrupters [*Environ Health Perspect* 2003; **111**: 255].

A new strain of *Bacillus thuringiensis* (**Bt**) toxin-expressing maize that is genetically modified to fight rootworm (a major crop pest) has been approved by the EPA, but scientists say the EPA is doing little to ensure that insects don't develop resistance to the insecticide that is produced by the plant [*Nature* 2003; **422**: 5].

Apr 2003 Open microscopy environment (OME) provides a first step toward biological image informatics [*Science* 2003; **300**: 100].

Beyond the Internet's present capabilities will be a global supercomputing network, "the Grid," designed to handle the ever-increasing flow of bioinformatics and physical science and imaging informatics [*Nature* 2003; **422**: 799]. We're talking about being able to handle *petabytes* (10^{15} bytes) of data per minute.

May 2003 The development of genetically-altered (transgenic) chickens that can lay eggs containing human proteins in their egg whites is a growing industry in the biotech world [*Science* 2003; **300**: 729].

The race to claim patents on the severe acute respiratory syndrome (SARS) virus raises questions about the patent system's ability to cope with fast-moving genomics projects [*Nature* 2003; **423**: 207 & 214].

The U.S. announced that it will ask the World Trade Organization (WTO) to declare that the *de facto* moratorium on approving new transgenic crops in the European Union is illegal. However, GM foods are not popular throughout Europe [*Nature* 2003; **423**: 369, 672].

The first **mule** has been cloned [*Science* 2003; **300**: 1354], and obviously the first race horse will be on its way shortly.

June 2003 *Inteins* are derived from so-called “junk” DNA that are translated into protein but then immediately removed. Among these spectacular proteins are enzymes that inject new DNA sequences into precisely-defined sites in a genome [*Science* 2003; **300**: 1646]. More than 400 papers on this exciting new breakthrough now appear in a database at www.neb.com/neb/inteins.html.

Although many are looking for allergic reactions in people eating GM food [*Environ Health Perspect* 2003; **111**: 1110, 1140], there is little if any evidence to support this.

Caspase-8 silencer RNA (**siRNA**) treatment in the intact mouse prevented acute liver failure-induced by an allergen as well as by a virus [*PNAS* 2003; **100**: 7797; *Nat Biotechnol* 2003; **21**: 629, 639]-raising hope for patients with acute liver failure.

Removing caffeine from coffee results in small amounts of unwanted chemical residues left behind; the process is also expensive and changes the flavor. A Japanese group, using RNAi (RNA interference) to knock down three enzymes in caffeine biosynthesis, has now produced coffee plants having a 50-70% decrease in caffeine content [*Nature* 2003; **423**: 823].

Human Gene Variability

A synopsis follows, of some of the more interesting findings reported, concerning how variable the human genome is, Jan - Jun 2003:

Jan 2003 Using a panel of **10 population-specific alleles**, Parra and coworkers were able to tell apart—with no overlaps—20 males of northern Portugal from 20 males on the west coast of Africa [*PNAS* 2003; **100**: 177]. Testing 173 subjects (regarded as “black”) from rural southeastern Brazil and 200 unrelated Brazilian “white” males in four major cities, it was then concluded that “color” (as determined by physical evaluation) is a poor predictor of African ancestry, as estimated by genomic markers.

Feb 2003 In contrast to the Brazil-Portugal study, a panel of **34 ancestry-informative markers** was applied to groups of African-Americans from Washington D.C., African-Caribbeans from Britain, and European-Americans from Pennsylvania [*Hum Genet* 2003; **112**: 387]. A high level of population structure related to admixture was found, but it was

concluded that “the individual ancestry of a person can be estimated, based on DNA analysis with a reasonable number of well-defined genetic markers.”

Mar 2003 How should one best study complex traits (which are the combination of more than one gene and the environment)? One way is classical genetics: to look at DNA sequence differences between individuals. The other is gene-expression analysis: to focus on variations in the genes being switched on. A systematic genome-wide analysis of the genetics of variation in gene expression was first demonstrated in budding yeast [*Trends Genet* 2001; **17**: 388; *Science* 2002; **296**: 752] and now has been extended to inbred mouse strains. Schadt and coworkers produced a genetically varying population of 111 mice, then used a microarray chip containing 23,574 genes and found 7,861 quantitative traits expressed in the population concerned [*Nature* 2003; **422**: 297, 260].

Several African peoples have a language that includes tongue-clicking. Mitochondrial DNA and Y chromosome analysis [*Science* 2003; **299**: 1977] suggest that the *San of Namibia* (formerly known as the !Kung) and the *Hadzabe of Tanzania* probably arose from a common ancestor about 112,000 years ago (plus-or-minus 40,000 years).

May 2003 Why do some people develop tuberculosis, while others do not, when both have been equally exposed to the bacterium? An elegant study of two inbred strains of mice (one susceptible, the other resistant, to *Mycobacterium tuberculosis* infections) has uncovered two loci on different chromosomes that offer resistance to tuberculosis infection [*PNAS* 2003; **100**: 6610]. This is another example of quantitative trait loci (**QTL**) mapping.

Jun 2003 It has become increasingly clear that all genes need standardized names across all species. An increasing number of journals, each year, are requiring approval of a gene name by the Human Genome Organization (**HUGO**) prior to publication of a submitted manuscript. Furthermore, the Human Genome Variation Committee (HGVC) is coordinating efforts to assess and standardize all genetic variation [*Nat Genet* 2003; **34**: 115].

Howard University’s Genomic Research in the African Diaspora (GRAD) biobank plans to collect DNA samples from 25,000 unrelated volunteers over the next 5 years—to probe how genetics and lifestyle factors might contribute to complex diseases [*Science* 2003; **300**: 1485].

Even if you are on the right track, you'll get run over if you just sit there.

ELSI...

Ethical, Legal and Social Issues

Tidbits from the first 6 months of 2003:

Jan 2003 For the second time in 4 months, a child has developed a leukemia-like disease after receiving gene therapy at the Necker Hospital for Sick Children (Paris). This brings to seven the total of clinical gene therapy studies “on hold” around the world [*Science* 2003; **299**: 320; *Nature* 2003; **421**: 678; *Nature* 2003; **422**: 7]. How “safe” is gene therapy?

Feb 2003 The death of **Dolly**, the first cloned sheep, is leading people to query about how “healthy and normal” cloned animals really are [*Nature* 2003; **421**: 776]. Ten out of 12 cloned mice died before their average natural life span of 800 days [*Nat Genet* 2002; **30**: 253], probably of pneumonia or liver disease—adding fuel to the fire.

Hormesis in dose-response curves, with regard to toxicity or cancer studies, demands a reappraisal of the way risks are assessed [*Nature* 2003; **421**: 691]. Dose-response models include threshold, linear non-threshold, and hormetic (protection at low doses, then manifestation of disease at higher doses).

Mar 2003 Now the United Kingdom wishes to have its own genetic database [*Nat Genet* 2003; **33**: 325]. Up to half a million Britons will be asked to contribute blood, undergo a medical examination, and fill out a questionnaire. After 10 years, more than 11,000 of the subjects are predicted to develop diabetes, 8,000 myocardial infarction, and between 3,000 and 6,000 cases each of breast, prostate and colorectal cancer.

Apr 2003 In rhesus monkeys [*Science* 2003; **300**: 297] and in unpublished studies of other primates [*Science* 2003; **300**: 225], cloning robs the embryo of key proteins that allow a cell to share chromosomes and divide properly—making the feasibility of cloning human and nonhuman primates far more difficult than cloning cattle, sheep, mice, rabbits and cats. Legislators can perhaps relax a bit.

The new regulations under the Health Insurance Portability and Accountability Act (**HIPAA**), regarding the privacy of medical records, went into effect on April 14th. Reams of more paperwork now need to be filled out by physicians, scientists and patients [*N Engl J Med* 2003; **348**: 1423, 1486].

May 2003 Why worry about the ethical problems surrounding stem cells being made from

human embryos, if stems cells from human exfoliated deciduous teeth [*PNAS* 2003; **100**: 5807] can become a resource?

Jun 2003 Although there are several textbooks and many review articles detailing the advances in pharmacogenomics, the recently released book (*Pharmacogenomics: Social, Ethical, and Clinical Dimensions*) edited by Mark A. Rothstein is the first comprehensive review of potential benefits and unwanted harm that could arise from the implementation of pharmacogenomics into public health practice [*Nat Genet* 2003; **34**: 123].

In the United Kingdom, a couple who had three babies die before 3 mo of age with sudden infant death syndrome (SIDS), was acquitted from murder by biochemical evidence to support a genetically-inherited mitochondrial disorder. The science-based defense was sufficiently robust to create reasonable doubt in the minds of the jury [*Science* 2003; **300**: 1858].

Gene-Environment Tidbits of Interest

Dec 2002 Nearly 20 years after the Seveso, Italy, accident (explosion in a factory leading to dioxin exposure to the surrounding community), plasma immunoglobulin G (IgG) levels—but not IgM, IgA, or complement C3 or C4—were highly statistically significantly ($P = 0.0004$) decreased in association with increased plasma dioxin concentrations [*Environ Health Perspect* 2002; **110**: 1169].

Feb 2003 Long, long ago Larry Snyder determined that the inability to taste phenylthiourea (PTU) and phenylthiocarbamide (PTC) was an autosomal recessive trait affecting about 30% of Caucasians in the U.S. [*Science* 1931; **74**: 151]. Thanks to the Human Genome Project and advances in cloning and DNA sequencing, it has now been shown that mutations in a member of the *TAS2R* bitter taste receptor family are responsible for 55-85% of the variance in PTC sensitivity [*Science* 2003; **299**: 1221]. Other mutations in this gene family, or modifier genes, must be the cause for the remainder of this variance [*Hum Genet* 2003; **112**: 567].

It is well known that cells can repair damaged DNA. Now—and perhaps not unexpectedly—it has been shown [*Nature* 2003; **421**: 859 & 795] that damaged RNA can also be repaired in the intact cell, and some of the same enzymes are involved.

Mar 2003 It is estimated that 3-4 million Americans under age 18 take psychiatric drugs, more than double the number of a decade ago [*Science*

2003; **299**: 1646]. In contrast to the beneficial short-term effect, however, one must be cautious about the children's lack of ability to concentrate in schoolwork, and the possible long-term effects—including tumors that might be induced by these therapeutic antagonists of biogenic amines [*Nature* 2003; **423**: 792].

Human *CYP1B1* defects are associated with primary congenital glaucoma (buphthalmos, a defect in newborns caused by increased pressure inside the eyeball). The *Cyp1b1*(-/-) knockout mouse, in combination with a defect in the tyrosinase gene (*Tyr*), exhibits abnormal drainage of fluid from the eyeball [*Science* 2003; **299**: 1578], underscoring the importance of modifier genes that influence the penetrance and expressivity of a particular genetic defect.

A panel of three genetic tests (factor V Leiden, prothrombin variant G20210A, and protein C deficiency) increased the predictive value of testing for venous thrombosis at least 8-fold [*Am J Hum Genet* 2003; **72**: 636], showing the importance of multiple disease-susceptibility-gene testing to improve the prediction of complex diseases.

Daily use of aspirin is associated with a significant decrease in the incidence of colon and rectal polyps, adenomas, and cancers [*N Engl J Med* 2003; **348**: 883].

Cigarette smoking is the greatest risk factor for emphysema, but only 15-20% of smokers develop emphysema—again suggesting gene-environment interactions. Genes encoding matrix metalloproteinases, transforming growth factors (TGFs), and downstream TGF-triggered signaling molecules [*Nature* 2003; **422**: 169 & 130] appear to be among the genes responsible for the development of emphysema.

Apr 2003 Agent Orange is a defoliant sprayed from airplanes during the Vietnam War, so that trees would lose their leaves, and is also sprayed along highways in some states as a form of weed control. Dioxin is a contaminant in Agent Orange that is known to cause birth defects and cancer. Recently released government reports now show that the total amount of dioxin contaminant sprayed during the war was as much as 4 times as great as was previously estimated [*Nature* 2003; **422**: 649].

Due to the severe acute respiratory syndrome (SARS) epidemic in Toronto, the American Association for Cancer Research canceled its April annual meeting there, rescheduling it for July in Washington, DC.

A new important redox cofactor, pyrroloquinoline quinone (PQQ), was first discovered in bacteria but now looks like it is also important in mammals [*Nature* 2003; **422**: 832].

Clinicians are pleading for clear clinical descriptions (phenotype) of affected individuals having mutations in a particular gene or genes, as

well as those clinically affected in whom mutations are not found [*Nat Genet* 2003; **33**: 440]. This represents the growing concern for the need of *phenomics*.

May 2003 The roles of BRCA1 and BRCA2 in error-free DNA repair by recombination [*N Engl J Med* 2003; **348**: 19] are becoming more and more clear in the quest for understanding inter-individual differences in susceptibility to breast cancer and other forms of cancer.

Progeria is a rare genetic disorder causing the child to age rapidly, dying by the second decade of life. Mutations in the autosomal recessive lamin A gene (*Lmna*) were found to cause progeria in a mouse model [*Nature* 2003; **423**: 298].

The activated dioxin-binding AH receptor directly associates with estrogen receptor- α and - β [*Nature* 2003; **423**: 545 & 487], which might help explain some of the endocrine disrupter functions of dioxin.

Jun 2003 Long ago it was proposed that most P450 enzymes that are regarded as “metabolizing drugs only” more than likely have endogenous substrates [*Mol Endocrinol* 1991; **5**: 1203], and CYP2D6 is among the “most drug-metabolizing” of them all. Putting the human *CYP2D6* gene into the mouse, Gonzalez and coworkers have recently found that CYP2D6 is the final enzyme in serotonin formation, and is a 5-methoxyindolethylamine *O*-demethylase [*Pharmacogenetics* 2003; **13**: 173 & 307]. Since there are CYP2D6 efficient (EM) and poor (PM) metabolizers, it is likely that this human polymorphism is relevant to certain neurological diseases such as depression or obsessive-compulsive disorders, as well as the handling of drugs used to treat these disorders.

As discussed in previous issues of *Interface*, in 1997 the appetite suppressant, fenfluramine, and a drug combination “FenPhen,” were removed from the marketplace because of many patients developing valvular heart disease. This proliferative effect can be duplicated in human cardiac valvular interstitial cells in culture, and the hallucinogen “Ecstasy” (3,4-methylenedioxymethamphetamine) also can cause this effect [*Mol Pharmacol* 2003; **63**: 1223].

Once again (how many times must we be assured of this?) there is no link between the risk of breast cancer and living near power lines [*Am J Epidemiol* 2003; **158**: 47].

Also related to the SARS epidemic, the June meeting of the International Union of Biochemistry & Molecular Biology (IUBMB) in Toronto was canceled and will be rescheduled elsewhere.

The *daf-2* gene in the nematode *Caenorhabditis elegans* is associated with longevity. Now it has been shown that *daf-2* mutant worms are resistant to bacterial pathogens [*Science* 2003; **300**: 1921].

Tidbits about Evolution....

Jan 2003 The dramatic symbiosis (living together in mutual advantage) between fungus-growing ants and the fungi they cultivate and the garden parasites over more than 50 million years of co-evolution has been documented by DNA sequences in all three organisms [*Science* 2003; **299**: 386].

Feb 2003 As the complete genome sequence of the chimpanzee is expected later this year, comparison of the human and other primate DNA sequences is helping us to define new genes, exons, and conserved regulatory regions [*Science* 2003; **299**: 1391].

Twelve populations of the bacterium *Escherichia coli* were allowed to “evolve” in a sugar-limited medium for 20,000 generations (~60 weeks). In humans, this would be the equivalent of evolution over 400,000 years. The expression profile of the ancestor was compared to that of two evolved populations, and the same 59 genes changed—and in the same direction—in both populations (relative to the ancestor). Many of the genes were in the sugar-energy pathway related to the selective pressure [*PNAS* 2003; **100**: 1072]. Here is an example of evolution “happening” before our eyes! And detected by DNA microchips!

Mar 2003 Evolution has used ancient pathways to create similar-looking signaling pathways. Although hormone structures in plants and animals may have common origins, the receptors that recognize them appear to have evolved independently after the two kingdoms diverged [*Nature* 2003; **422**: 122].

By examining the DNA from *Helicobacter pylori*, a chronic stomach pathogen of humans and sometimes the cause of stomach cancer, seven populations with distinct geographical distributions were found—which reflected human migrations involving the prehistoric colonization of Polynesia and the Americas, the neolithic introduction of farming to Europe, the Bantu expansion within Africa, and the slave trade [*Science* 2003; **299**: 1582].

What is the “universal ancestor,” the first living thing that gave rise to all bacteria and then all plants and animals? Molecular analysis of conserved sequences in the ribosomal RNAs of modern organisms (whose genomes have been sequenced) reveals a three-domain phylogeny (genes common to animals, plants and bacteria) that converges in a universal ancestor for all life [*Genome Res* 2003;

13: 407]. Of the nearly 3100 clusters of orthologous groups (COGs) in the database, only 80 were universal and only 50 were three-domain.

We know that animals, and even plants, have genes that respond to day-night cycles (circadian rhythm). Members of the archaeobacteria and eubacteria kingdoms also have circadian pacemakers which have evolved in parallel with the geological history of the earth [*PNAS* 2003; **100**: 2495]—and are distinctly different from the “clock” genes in animals and plants.

Apr 2003 Chromosomal rearrangements within species are believed to contribute to reproductive isolation and, hence, formation of new species (*speciation*) [*Science* 2003; **300**: 267 & 321]. By “un-rearranging” yeast chromosomes to break down a species barrier, this hypothesis has now been proven [*Nature* 2003; **422**: 25]. In a fruit fly study, Presgraves and colleagues found a gene on *Drosophila simulans* chromosome 3 that interacts with one or more unknown genes on the *Drosophila melanogaster* X chromosome—causing death of male hybrid offspring; in either of the two individual species, the gene products function normally [*Nature* 2003; **423**: 715 & 699]. This is the latest most exciting study of speciation.

May 2003 In past issues of *Interface*, we have discussed the likelihood that Neanderthals co-existed with modern Europeans until perhaps 29,000 years ago and cross-breeding appeared unlikely. Further data in support of this tenet was obtained from mitochondrial DNA (mtDNA) hypervariability region I from two modern *Homo sapiens* subjects, dated at 23,000 and 25,000 years ago [*PNAS* 2003; **100**: 6593].

Evolution—more rapid than expected—can be triggered by sudden changes in a species’ environment. Several examples with fish (guppies in 1997, Atlantic silversides in 2002, and salmon in the less stressful environment of a hatchery in 2003) are discussed [*Science* 2003; **300**: 895].

Comparing mtDNA from museum skins of mice caught in the Chicago area since 1855 and from modern mice trapped alive in the same area [*Nature* 2003; **423**: 397], the mammalian mitochondrial genome was found to have undergone rapid evolution.

Jun 2003 In recent issues of *Interface*, we described the Chad skull and how it fits into the overall picture of human migration out of Africa. Further evidence (newly discovered fossils from Ethiopia) has recently strengthened the “Out of Africa” model for the origin of modern humans [*Nature* 2003; **423**: 692; *Science* 2003; **300**: 1641].

The shift once again is toward East Africa.

Comparing ~90 kb from 97 human genes with their counterparts in available sequences from chimpanzee, gorilla, orangutan, Old World monkey and mouse, it was concluded that the most recent common ancestor of humans and chimpanzees lived 5-6 million years ago (MYA), whereas the human-chimpanzee clade separated from the gorilla clade 6-7 MYA [*PNAS* 2003; **100**: 7181]. These findings are illustrated in **Figure 2**.

An *absolutely excellent* illustration of the Tree of Life, based on the latest DNA sequence comparisons, can be seen in the June 13th issue of *Science* 2003; **300**: pp 1694-95. This is part of a Special Section on Evolution.

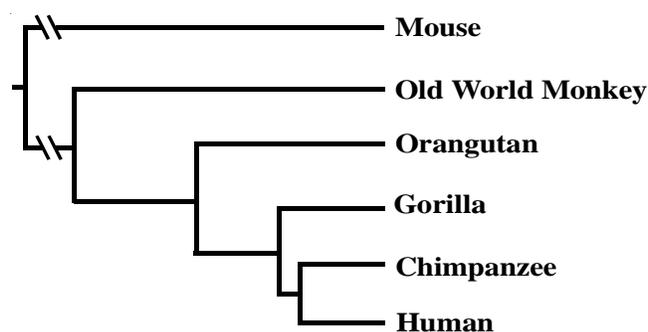


Fig. 2. The most parsimonious tree of 97 genes from five primates plus the mouse. The five branches at bottom are drawn to proportion, but the mouse branch should be more than 13 times longer.

Ecogenetics Research Core SPONSORED SPEAKERS

John Stegeman, Chair, Dept of Biology, Woods Hole Oceanographic Institute (MA)
30 Apr 2003 "*Uncoupling of cytochrome P450 1A enzymes: a possible mechanism in the toxicity of planar halogenated aromatic hydrocarbons.*"

Peter O'Brien, Professor, School of Pharmacy, University of Toronto (Ontario, Canada)
14 May 2003 "*The good, the bad, and the ugly antioxidants--in our diet, lifestyle and environment.*"

Vasilis Vasiliou, Associate Professor, School of Pharmacy, University of Colorado (Denver, CO)
28 May 2003 "*Protective role of corneal ALDH3A1 against oxidative stress.*"

Dean Jones, Professor of Biochemistry, Emory University (Atlanta, GA)
4 June 2003 "*Thioredoxin, glutathione and cysteine: distinct nodes in the circuitry for redox signaling.*"

CEG WORKSHOPS AND EVENTS

**Public meeting to discuss
Breast Cancer & the Environment
Research Center**
March 8 2003
Sponsored by COEP

All-day CEG Workshop
March 21 2003
Jointly sponsored by Genetic Epidemiology
and Biostatistics, and the
Human Populations Cores

Protein Analysis Workshop
April 3 2003
Sponsored by the **NEW**
Protein Analysis F&S Core

**Workshop: Surviving in the
Post 9/11 World**
June 9 2003
Sponsored by
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The Environmental Policy Center
Molecular Epidemiology in
Children's Environmental Health
Department of Environmental Health
Cincinnati Children's Environmental
Health Center
Ohio State University Environmental Health
Sciences

Life is not about how
fast you run, or how
high you climb, but how
well you bounce.

web-cytes

In the mid-19th century Johann Wolfgang von Goethe wrote a romantic poem, entitled *Gingko biloba*, and sent a copy to Marianne von Willemer, on which he pasted gingko leaves:

<http://www.xs4all.nl/~kwanten/name.htm> This is believed to be the first recognition by anyone that the gingko was neither a monocotyledon (e.g. corn, grass) nor a dicotyledon (e.g. maple leaf, oak leaf)—but, rather, something in between. Gingko represents a common ancestor from more than 100,000 years ago. Brush up on your german first, because this site is written *auf deutsch*.

To keep tabs on the baseball playoff races, there is a Remote Interactive Optimization Testbed (RIOT) project at UC Berkeley

<http://riot.ieor.berkeley.edu/~baseball> which takes into account a lot more than win-loss records. Factored in are which games yet to be played with whom, so sometimes a team can be eliminated from the playoffs, the win-loss record notwithstanding.

Do you need a good primer on genome research and its possible impact on medicine and society?

This one is good for students and the public.
<http://www.wellcome.ac.uk/en/genome/> or
<http://www.wellcome.us/en/genome/>

How is genetics transforming medicine? For simple overviews focusing on basic inheritance, genetic engineering, the Human Genome Project, gene therapy, and other related topics, check out:
history.nih.gov/exhibits/genetics

Started 3 years by a group of fully-clothed medical students at the University of Cambridge, this web site offers a mix of science news, interviews with researchers, answers to listeners' questions, useful links, book reviews, and even a chat room.
www.thenakedscientists.com

Developmental biologists and marine researchers can see how starfish and other marine inverte-

brates begin life with this atlas from the University of Saskatchewan, Canada.

<http://scaa.usask.ca/gallery/lacalli/tutorial>

The Integrated Risk Information System (IRIS) is an essential resource for anyone looking for authoritative safety information on hazardous environmental chemicals.

www.epa.gov/iris

For music, carrying tunes at least partially composed by translating DNA sequences into musical notes, check out:

www.dnamusiccentral.com

This site summarizes more than 100 databases—from government, university and private sources—concerning different forms of transportation and their social and environmental costs. For example, would you like to know the air-quality index for lead, sulfur dioxide, particles and ozone in dozens of American cities and towns since 1996?

www.transtats.bts.gov

Effective as of 14 Apr 03, there are new federal regulations that strictly limit the release of patients' medical information. Find out if the new privacy rules affect you.

<http://privacyruleandresearch.nih.gov/default.asp>

A Freudian slip is.....
when you say one thing
but mean your mother.



Apparently a teacher has been arrested in the UK in possession of compasses, protractor, and straight edge. It is claimed he is a member of the Al Gebra movement bearing weapons of math instruction.



LETTERS TO THE EDITOR

RESPONSES/COMMENTS TO VARIOUS QUESTIONS

COMMENT In addition to our tribute to Professor Roy E. Albert in the last issue of *Interface*, see Mort Lippmann's article, "Scientific contributions of Roy Ernest Albert (1924-2002), a pioneer in radiation risk assessment and its application to public policy." *Radiat Res* 2003; **160**: 124-129.

Q My husband says that I should not smoke because it makes my arthritis worse. I don't think he knows what he is talking about, but thought I should ask you.

A Your husband might be correct. There is evidence that—even if patients have ever smoked cigarettes, even if they now have quit—they are more likely to have a more severe form of rheumatoid arthritis than patients who have never smoked. The effect seems more pronounced in women than in men. Obviously, arthritis is a manifestation of the combination of genetic predisposition and environmental factors. One gene appears to be glutathione S-transferase-mu (*GSTM1*), which encodes an enzyme that degrades many active metabolites of chemicals in cigarette smoke [*Arthritis Rheum* 2002; **46**: 640]. Another gene-gene interaction includes the *HLA-DRB1* and tumor necrosis factor (*TNF1*) genes [*J Rheumatol* 2002; **29**: 2313].

COMMENT The issue of "water" has been discussed in previous *Interface* issues. Over a billion people in the world do not have access to clean water, and the situation is getting worse—predicting there might be worldwide increases in waterborne infections and malnutrition [*Nature* 2003; **422**: 251].

Q What's the latest about the human being that was supposedly cloned? Was it, or wasn't it?

A Clonaid, the company associated with the Raelian cult that announced last December it had cloned a human, seems to have no lab space and only two employees. The company is little more than a website [*Nature* 2003; **423**: 8]. A lawyer filed a suit in a Florida court, asking that a guardian be appointed for "Eve" (the child that Clonaid claims is a human clone), and a subpoena was served on the Clonaid vice president. Clonaid claimed the child clone is now in Israel, prompting the Florida court to close its case. Given our comments about **cloning difficulties in primates** (see "ELSI, April 2003" in this issue), however, it appears more and more likely that this whole claim by Clonaid is fraudulent.

Observations by a Biologist

Crab-Spiders, Coral Reef Fish, and Monarch Butterflies

The color of some European species of **crab-spider** is the same as the color of the flower that it seeks as a habitat, no doubt a mechanism to camouflage them from predators as well as their intended prey. In contrast, although the color of the Australian crab-spider (*Thomisus spectabilis*) is impossible to see on the white daisy (*Chrysanthemum frutescens*) to the human eye, it is highly conspicuous to honey bees that are sensitive to ultraviolet (UV) light [*Nature* 2003; **421**: 334]. These scientists from Austria, Australia and London showed there were no olfactory cues or blue or green light stimuli from the crab-spider that excited honeybee color-receptors, meaning that only the UV light is what attracts the honey bees to this flower. The crab-spider appears to be exploiting the honeybee's preexisting preference for flowers with color patterning, thereby helping the flower to become pollinated; and the crab-spider, however, does not bother the honeybee.

It turns out that the crab-spider's color also helps him attract his food, which is the *stingless bee*. The stingless bee, which also perceives ultraviolet light, is attracted to the daisy, and *becomes the victim*. This is another fascinating example of how genes encoding a trait have evolved, relative to the organism's *environment*—which in this case includes the flower, the honeybee, and the crab-spider's food, the stingless bee.

Researchers of coral reefs have long wondered how **coral reef fish** larvae—as small as 1 or 2 cm—can find a suitable reef on which to settle, after being tossed out to sea by the tides. It turns out that humans are not the only ones who can learn the sound of a mother's voice while still in the womb. From inside their eggs [*Science* 2003; **299**: 341], larvae of some species of coral reef fish apparently can identify the sounds of home and family!

Embryos appear to “imprint” on the squeaks, grunts and whistles of their parent, and the hatchlings use tiny stones in their heads (called *otoliths*) to pick up the racket and zero in on home. This group at the Australian Institute of Marine Science in Darwin (Australia), with collaborators in England and Kentucky, had previously shown that hatchlings are attracted more than twice as often to experimental reefs where underwater speakers play reef sounds, compared with reefs where there are no sounds. This is another interesting example of *genes* evolving in combination with the *environment*.

Every autumn, **monarch butterflies** (*Danaus plexippus*) migrate thousands of miles from eastern North America to central Mexico, where they winter over. Although it is presumed that the butterflies use a time-compensated sun compass to navigate, it is now being realized that the insect's circadian clock interacts with the sun compass—enabling these remarkable migrants to maintain a southwesterly flight bearing—as the sun moves across the sky each day.

Investigators at the University of Massachusetts Medical School [*Science* 2003; **300**: 1303] used a flight simulator in their lab, under three lighting conditions, and followed the expression of the periodic gene (*Per*), known to be an essential component of the circadian clock in the fruit fly. They could examine their tethered migrants and observe the effects of changing the day-night cycle, UV light versus regular light, and the arc of the “sun” (in the simulator) at that time of the year in eastern North America versus that in central Mexico! The scientists found that constant light destroyed the insects' circadian rhythm (at both the behavioral and molecular level) but did not affect their orientation direction relative to the “sun.” The orientation direction depended on UV light from the “sun” for navigation, whereas UV did not affect circadian rhythm. Reppert and coworkers concluded that the butterflies' UV-independent circadian clock is necessary but not sufficient for successful migration; in addition, there are distinct light-input pathways for the stimulation of UV-dependent oriented flight behavior. Next, we need to understand this “clock-compass” interface. This is, yet, a third great example of *gene-environment interactions* pursuant to an evolutionary advantage.

SCIENCE LITE

According to an English university study, the order of letters in a word doesn't matter, the only thing that's important is that the first and last letter of every word is in the correct position. The rest can be jumbled and one is still able to read the text without difficulty.

If you can read the text above, your brain is demonstrating the remarkable ability to force patterns on even jumbled messes.

A quick search on PubMed brought up articles related to this phenomenon addressing the effect of font regularity, upper and lower case, first letter in a word recognition, and asymmetry vs letter components of a word, recognition time for letters and nonletters, serial position, array, letter size, and processing order e.g. *J Exp Psychol Hum Percept Perform* 1982; **8**: 724)

“Smoking kills. If you're killed, you've lost a very important part of your life.”
---Brooke Shields.

“It isn't pollution that's harming the environment. It's the impurities in our air and water that are doing it.”
---Al Gore, Vice President

“We've got to pause and ask ourselves: How much clean air do we need?”
---Lee Iacocca

“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.”
---name withheld.

to get=status; to do=success; to be=significance

SCIENCE ^{not so} LITE

England is old and in some small villages the locals started running out of places to bury people. They would dig up coffins and take the bones to a bone-house and reuse the grave. When re-opening coffins, 1 out of 25 coffins were found to have scratch marks on the inside. Realizing they had been burying people alive, they came up with the thought of looping a string around the wrist of the corpse, through a hole in the coffin, and up through the ground attached to a bell. Someone had to sit in the graveyard all night (the “graveyard shift”) to listen for the bell; thus, someone could be “saved by the bell” or was considered a “dead ringer.”

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What the world really needs is a computer that can figure out all the things in life that don't add up.

Pilot Project Recipients 2003

Michael T Borchers PhD, Department of Environmental Health. *“CD8+ cells in chronic obstructive pulmonary disease”*

Iain Cartwright, PhD, Department of Molecular Genetics. *“Expression profiling of arsenic susceptibility variants”*

Ranjan Deka, PhD, Department of Environmental Health. *“Genetics of type-2 diabetes-related phenotypes in adolescents: Development of a resource”*

Kathleen Dixon, PhD, Department of Environmental Health. *“DNA damage-induced phosphorylation and interactions between BLM and RPA”*

Mary Beth Genter, PhD, Department of Environmental Health. *“Mechanism and gender specificity of naphthalene carcinogenicity”*

Gurjit Khurana Hershey, MD, PhD, Division of Asthma and Allergy, Children’s Hospital Medical Center. *“Gene-environment interactions in asthma outcome”*

Dan Nebert MD, Department of Environmental Health. *“Association between the AHR genotype and risk of head- and neck cancer among smokers”*

Yolanda Sanchez, PhD, Department of Molecular Genetics. *“The role of Sfp1 in the response to DNA damage”*