



# INTERFACE:

## GENES AND THE ENVIRONMENT

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### *Effects During Pregnancy Can Cause Disease in Adulthood*

For centuries, philosophers, historians, scientists and theologians have discussed *predestiny* (i.e. has “what will happen” been predetermined?). In fact, the concept of “predestiny,” or “fado” (fate) and our thinking of genes as if they were the unpredictable genetic determinants from which we cannot escape was discussed in issue #1 of *Interface*. In this article we discuss things that happen to the embryo and fetus *in utero*, which might affect the health of that individual—decades later as an adult, but sometimes have been attributed to fate.

The effects to be described below must be distinguished from “classical” birth defects. For example, a mother given thalidomide during her pregnancy sometimes delivered a child with deformities of the limbs (usually arms); consequently,

this drug was removed from the market. A mother who imbibes too much alcohol during her pregnancy has an increased risk of delivering a baby with “fetal alcohol syndrome” (FAS; which includes defects of the face, hands, heart and brain, often with mental retardation). In the topic discussed here, we describe some examples of disorders that are not apparent at birth.

#### *The Diethylstilbestrol (DES) Story*

Starting in 1938, DES was sometimes given to women in early pregnancy—at first if there was any history of several miscarriages, but in the 1950s as “basic hormonal support” to help produce healthier babies (**Figure 1**). Then came several reports in the 1960s of an extremely unusual type of cancer: vaginal anterior wall clear-cell adenocarcinoma (CCAC). When a “cluster” of cases of an unusual disease happens, not only is there concern but also a need to search for the underlying cause of the disease. Epidemiologists found that the common link in these young women is, that during their first trimester in utero, their mother had taken DES. More than 4 million women in the U.S. alone and many more in Europe and Australia had taken DES by the time it was finally removed from the market in 1971. Fortunately, this unusual type of cancer occurs in only ~0.1% of women whose mothers had taken DES.

Unfortunately, the far more prevalent effects of DES—deformed reproductive tracts and therefore gynecological problems and infertility—were subsequently realized when the thousands of DES daughters were being carefully screened for CCAC.

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**Figure 1. Advertisement from 1957**

Abnormalities of the vagina, cervix and uterus were responsible for an increased risk of adverse reproductive outcomes in DES daughters. Whereas more than half the DES daughters can eventually experience a live birth, this becomes less likely in women with genital tract abnormalities; in these women there is a two-thirds chance that each pregnancy will be unsuccessful. In DES sons, the clinical data include male reproductive problems such as *cryptorchidism* [undescended testis], epididymal cysts, retained Müllerian ducts, and decreased fertility. There are rare reports that *daughters of the DES daughters* have developed CCAC...!!

The DES story, then, is the first example of a gene-environment (really, a gene-drug) interaction in which genes during development of the reproductive tract are affected by a drug. DES is regarded as an agonist of estrogen, and therefore the normal hormone cannot bind properly to its receptor and evoke the normal developmental changes in the reproductive tract of the embryo at the appropriate time. DES might thus be considered the first recognized *endocrine disruptor*.

### **Minimata Disease**

Due to eating seafood polluted by industrial waste in Japan, epidemics in Minamata Bay in 1956

and Niigata in 1965 were reported where many infants with “cerebral palsy” were born. Methylmercury was found to be the cause. The 638 patients certified to have Minimata Disease displayed mental retardation, spasticity, inability to walk, poor balance control, hearing loss, and skin pigmentations. These patients are still being followed clinically today.

Methylmercury can be toxic or lethal to any child or adult. What sets this disease apart from regular organic mercury exposure was that this disease was caused by tainted seafood eaten by the mother during her pregnancy with the victim. And it was often a very serious, extremely undesirable outcome. The number of less massive exposures to methylmercury, and borderline effects on health and mental status of the resulting children, are unknown.

### ***Polybrominated Biphenyls (PBBs) In Utero and Disease***

In 1973 hundreds of individuals (on 308 farms) in southern Michigan were accidentally exposed to about 1,000 pounds of PBBs. The fire retardant *Fire-Master* had been mistaken on a shipping dock for the cattle food *Nutri-Master*, and thousands of cows, pigs and chickens consumed this chemical and had to be destroyed. Humans ate the meat, milk and eggs before the magnitude of the danger had become clear. PBB levels (370 times higher in adipose tissue than in blood) are still decreasing in this exposed population at a rate of 7% per year. Some of the earliest clinical signs included *amnesia*, *confusion* and *somnolence* (farmers lost their tractors, were unable to find their way home at the end of the day, and fell asleep in the fields) and *leukocytopenia* (low white blood cells). Also reported was chloracne—a skin rash involving sebaceous (oil) glands and a hallmark sign of [aryl hydrocarbon receptor (AHR)-mediated] toxicity in dioxin-exposed workers. This topic was covered in *Interface* issue #14.

Besides the toxicity to children and adults, what is central to the theme of this article is that low birth weights, increased respiratory illnesses, and the possibly a slight lowering of I.Q. among children who were in utero at the time (1973-75) of the PBB exposure also were found. The mental development

of these children continues to be followed into adulthood. Again, PBBs can be toxic to anyone, but exposure to PBBs in utero can also lead to health problems later in life.

### ***Polychlorinated Biphenyls (PCBs) In Utero and Disease***

Hyperactivity and changes in behavior have been reported in children whose mothers had massive exposures to PCB-contaminated rice bran oil during pregnancy. This was called *Yusho disease* (Japan in 1968) and *Yu-cheng* (Taiwan in 1979). In northern Kyushu (Japan) about 2,000 people were poisoned by PCBs and polychlorinated dibenzodifurans (PCDFs, pyrolysis products of PCBs) in contaminated rice oil. The major symptoms of Yusho disease were skin and eye lesions, but some other symptoms (e.g. irregular menstrual cycles, altered immune responses) suggest that PCBs have endocrine-disrupting activities. In the case of Yu-Cheng, children exposed to PCBs in utero and through their mothers' milk were reported to have intellectual impairment.

A significantly lowered I.Q. has also been determined in children born to women who had eaten large amounts of fish contaminated with PCBs in the Great Lakes Region of the U.S. Again, the recurring theme is environmental exposure—in utero—affects the child and adult later in life with serious disease.

### ***“Resetting” the Rheostat for the Cardiovascular System***

This example is in laboratory animals but has incredible ramifications, if it might also happen in humans. In the 1950s Goldblatt showed that he could induce *hypertension* (high blood pressure) in the adult rat by clamping off one kidney. Further, in the pregnant mother the renal clamp induced hypertension in her pups—after they were born and grew up. Nothing happened to the pups if the father was given a renal clamp—confirming that this “*cardiovascular re-programming during a critical embryonic or fetal window*” reflected the physiological triggering of a “*set-point system*” in the maternal-fetal unit.

In young spontaneously hypertensive (SH) rats, Harrap and coworkers found that angiotensin-converting enzyme (ACE) inhibitors lowered blood pressure, and that the accumulation of *bradykinin* (a small protein that binds to its receptor and may help control blood pressure) might contribute to these long-term effects. Taking the rats off ACE inhibitors several months later—results in higher blood pressure, but not as high as in untreated control age-matched rats [*Hypertension* 1995; **25**: 162]. Since the effect was more dramatic, the younger the animal at the start of the treatment, and depended on the size of the *renal medulla* (inner portion of the renal cortex), the obvious question arose as to whether ACE-inhibitor treatment might also work during pregnancy. Harrap's laboratory then showed that *ACE inhibitors, given to the mother during pregnancy, cured hypertension in the pups*—adding further fuel to this idea of critical cardiovascular reprogramming in utero.

The implications of these experiments are enormous. Should mothers, from all families in which high blood pressure is known to be a problem, be routinely treated with ACE inhibitors—during pregnancy—so that the resulting child, and especially the adult three or six decades later, might be prevented from having serious cardiovascular disease?

### ***Maternal Stress and Disease in the Offspring***

Although birth weight is a crude measure of fetal growth, some researchers have been carrying out association studies of birth weight and maternal stress, placental development, or the quality of embryo implantation [*Science* 2002; **296**: 2167]. Babies weighing less at birth were found to be more likely to die of heart disease, and had about half the chance of developing breast cancer, as adults. If the placenta is poorly formed and does not remodel properly, the child later in life is more prone to high blood pressure. Some feel that stress in the mother leads to increased levels of stress hormones in the fetus, which resets the baby's hypothalamic-pituitary-adrenal axis such that the child is more likely to develop high blood pressure or type II diabetes later in life.

### ***Socioeconomic Status (SES) and Disease***

Kaplan and Manuck [*Ann N Y Acad Sci* 1999; **896**: 145] reviewed the subject of socioeconomic status (SES), stress, and atherosclerosis. Dominant male monkeys develop high serum lipids and more extensive atherosclerosis than subordinate males when housed in unstable, but not in stable, social groups. In contrast, subordinate females develop greater atherosclerosis than dominant females—irrespective of their conditions of SES. Kaplan and Manuck suggest that their findings may be informative in studying cardiovascular and other diseases in patients experiencing social stratification (*i.e.* disease incidence varying as a function of class membership within a population).

Taking these findings one step further, what happens to the developing embryo and fetus in the uterus of a subordinate female who is subjected to these subtle types of environmental signals? Would SES and stress—in the mother—contribute to disease later in the life of these offspring? Would differences in rates of cardiovascular disease, and perhaps diseases of other organ systems, be higher in communities suffering from poverty and oppression?

### ***Conclusions***

It seems clear that drugs and other environmental chemicals, as well as the cardiovascular make-up of the mother at the time of the pregnancy, can affect the developing embryo or fetus such that certain types of disease are more likely to happen later in life. Organ systems that appear to be most commonly affected include: the central nervous system (CNS) and the immune, endocrine, and cardiovascular systems. With our ever-expanding knowledge about the human genome, developmental biology, and the new molecular genetics techniques such as cDNA and protein microarrays, we should soon learn a lot more about the mechanism of this “in utero programming” and perhaps ways to prevent it from happening to future generations of children.

—Contributed by Dan Nebert.



## **Newly Created Center for Genome Information**

Ranjit Chakraborty, PhD, an internationally distinguished geneticist, joined the University of Cincinnati Medical Center’s Department of Environmental Health and has created the Center for Genome Information (CGI). Li (Felix) Jin, PhD, director of the genotyping core laboratory of the CGI, has set up a facility (Jun 2002) including a computational biology laboratory that is capable of examining 500,000 single-nucleotide polymorphisms (SNPs) per week. The CGI mission is to establish a research program for understanding the genetic basis for complex diseases such as cancer, diabetes, obesity, Alzheimer disease, and Parkinson disease.

**Beware of what you set  
your heart upon, for  
surely it shall be  
yours.....**

*Ralph Waldo Emerson (1803-1882)*

# Home is where you hang your @

## Biotechnology, ...

What follows is a synopsis of some of the more interesting things that have happened during the first 6 months of 2002, with regard to genetically-modified (GM) plants, biotechnology, and related topics, provided chronologically:

**Jan 2002** As elegantly summarized in a list of published and unpublished data about cloned cattle, sheep, goats, pigs and mice [*Nature Biotechnol* 2002; **20**: 13], the idea that most cloned animals develop abnormally “is currently unjustified on scientific grounds and should not be used by policymakers or other groups as an argument to ban all human cloning research.”

The jellyfish green fluorescent protein (GFP)—and its improved variants, enhanced GFP (EGFP), cyan (CFP), and yellow (YFP)—are widely used *reporter genes* in pure and applied biological research. Now comes **DsRed** from the coral *Discosoma*, which is ideal for dual-color experiments with derivatives of GFP [*Nature Biotechnol* 2002; **20**: 83, 87].

Mutations in the *adenomatous polyposis coli* (*APC*) gene that cause colon and rectal cancer can be detected in fecal DNA from patients with relatively early tumors [*N Engl J Med* 2002; **346**: 311], suggesting a new approach for early detection of these types of cancers.

PPL Therapeutics (the company in Scotland that cloned Dolly the sheep) announced the birth of five piglets having the  $\alpha$ -1,3-galactosyltransferase gene disrupted. Humans (who lost this enzyme during evolution) recognize this sugar as foreign and kill transplanted pig organs in minutes, so the idea is that organs from these knockout pigs might not be rejected by the human immune system [*Nature* 2002; **415**: 103; *Nature Biotechnol* 2002; **20**: 109].

*Hoxb8*(-/-) knockout mice groom themselves to the point of creating large bald spots and lesions

[*Neuron* 2002; **23**: 23]. Since the *HOXB8* gene is strongly expressed in a particular brain region in patients with obsessive-compulsive disorder (OCD), there could be a relationship between this gene and “OCD-like” behavior in these null mice.

**Feb 2002** What is the extent of GM foods so far? Answer: herbicide- and insecticide-resistant soybeans, corn, cotton, and canola; a virus-resistant sweet potato; rice with increased iron and vitamins; and a variety of plants able to survive weather extremes. Soon, we will see: bananas that produce human vaccines against infectious diseases such as hepatitis B; fish that mature more quickly; trees that yield fruits or nuts years earlier; and plants that produce new plastics with unique properties. [www.ornl.gov/hgmis/elsi/gmfood.html](http://www.ornl.gov/hgmis/elsi/gmfood.html)

The first cat (named “copycat”) was successfully cloned [*Nature* 2002; **415**: 859]. Because it has a much cuter face (than cows, sheep, pigs, mice), this cat is going to encourage more cloning of family pets.

Fortunately, (for scientists who do not want even more paperwork and therefore would be unable to do as much scientific work) the senate turned down a bill that wanted to change a 30-year-old USDA policy exempting mice, rats and birds from regulation under the Animal Welfare Act [*Science* 2002; **295**: 1441].

**Mar 2002** Are cloned animals as healthy as regular animals, or not? The mice cloned several years ago are now being found to exhibit excess obesity [*Nature Med* 2002; **8**: 262] and a shortened life span [*Nature Genet* 2002; **30**: 253].

GM canola “superweeds,” resistant to three different herbicides, have been discovered in Canada—underscoring the potential problems of cross-pollination and/or *horizontal gene transfer* (or capture) of GM transgenes to unwanted volunteer plants nearby. One possibility might be to bring back the “terminator-like approach” (discussed in earlier issues of *Interface*), which would kill GM plants rather than allowing them to reproduce [*Nature Biotechnol* 2002; **20**: 210, 212].

**Apr 2002** Previous issues of *Interface* have discussed the problem of declining numbers of frogs and numerous deformities in amphibians—especially in the Great Lakes region, but really worldwide. The latest suggested culprit is *atrazine*, the most

commonly used herbicide in the U.S. [*PNAS* 2002; **99**: 5476]. Atrazine was shown to disrupt sex steroid pathways, which qualifies it as an *endocrine disruptor* [*Science* 2002; **296**: 447; *Nature* 2002; **416**: 665].

The latest mammal to be successfully cloned by nuclear transfer from adult somatic cells, is the *rabbit* [*Nature Biotechnol* 2002; **20**: 366].

According to data from Norway and elsewhere, *farmed fish* are escaping and sometimes overwhelming the gene pools of natural fish. Where farmed fish mingle with natural ones, 30% less offspring make it from the breeding grounds to the ocean. The negative effects of hybridization are not usually apparent until the second generation, when the co-adapted genes (“that tell the fish when to breed and how to find food”) become separated [*Nature* 2002; **416**: 571].

**May 2002** *Streptomyces coelicolor* represents the soil-dwelling filamentous bacteria responsible for producing most natural antibiotics. Its genome of 8,667,507 bases [*Nature* 2002; **417**: 141] includes 7,825 *predicted genes*—the largest number so far discovered in a bacterium.

Researchers are making transgenic mosquitoes with a decreased capacity to transmit the malaria parasite [*Nature* 2002; **417**: 387, 452]. If these could eventually be sent into the areas of the world that are endemic for malaria, this would greatly improve human health.

Chemicals were isolated that seem to provoke ants to attack and kill one another [*Nature* 2002; **417**: 505]. These turned out to be long-chain hydrocarbons. Hmmm. Could these be used as an alternative to poisons and repellants to control pesky ants..?

The Government of India has approved the commercial planting of its first GM crop: cotton, protected against bollworm by the *Bacillus thuringiensis* (Bt-cotton). About a dozen farmers’ organizations in their country demanded that the government reverse this decision by their Genetic Engineering Approval Committee, charging that this is a move “to dislodge small farmers” and a sell-out to the multinational companies [*Nature Biotechnol* 2002; **20**: 415].

**June 2002** Researchers have developed a *dwarf grapevine* by introducing mutant genes that make the “L1” plants shorter and stockier, plus two

genes that control the activity of the hormone gibberellin [*Nature* 2002; **416**: 847; *Nature Biotechnol* 2002; **20**: 565]. The result is a plant that is far smaller and much more fruitful than its progenitors. Soon, wine-makers will be able to make more wine using fewer plants, taking up less space.

Biotechnology remains a high-risk endeavor. Portfolio companies ended the 2001 year \$5.3 billion in the red [*Nature Biotechnol* 2002; **20**: 551].

A fresh security clampdown in U.S. universities and research institutions concerns how radioactive materials used in research and medicine are handled [*Nature* 2002; **417**: 776]. One of the terrorist suspects being held had apparently intended to build a “dirty bomb,” meaning a conventional bomb encased in (low) radioactive materials—which would make the victim population psychologically concerned for years (instead of hours) after the explosion.

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## Inner Strength

If you can start the day without caffeine or pep pills,  
If you can be cheerful, ignoring aches and pains,  
If you can resist complaining about your troubles,  
If you can be grateful for the same food day after day,

If you can understand when loved ones are too busy to give you time,

If you can forgive people who take things out on you when, through no fault of yours, something goes wrong,

If you can take criticism and blame without resentment,

If you can face the world without lies and deceit,

If you can conquer tension without medical help,

If you can relax without liquor,

If you can sleep without the aid of drugs,

**then.....**

**you are probably a cat or a dog!!!!!!**

modified slightly from the internet



# SCIENCE LITE

## Computers -- in the mode of Dr

**Seuss**  
If your cursor finds a menu item followed by a dash,  
and the double-clicking icon puts your Windows in the trash,  
and your data are corrupted 'cuz the index doesn't hash,  
then your situation's helpless and your system's gonna crash.

If a packet hits a pocket on a socket on a port  
and the bus is interrupted at a very last resort  
and the access of the memory makes your floppy disk abort  
then the socket packet pocket has an error to report.

When the copy of your floppy's getting sloppy on the disk  
and the macro code instructions cause unnecessary risk  
then you'll have a flash of memory and you'll want to RAM your ROM  
quickly turn off the computer 'cuz the system's gonna bomb.

If the label on the cable on the table at your house  
says the network is connected to the button on your mouse  
but your packets want to tunnel to another protocol  
that's repeatedly rejected by the printer down the hall  
and your screen is all distorted by the side effects of gauss  
so your icons in the window are as wavy as a souse  
then you may as well reboot and exit with a bang  
'cuz sure as I'm a poet the sucker's gonna hang!

*from the cincinnati fax news 6/12/02 with modifications.*

**Abdicate (v.), to give up all hope of ever having a flat stomach.**

**Balderdash (n.), a rapidly receding hairline.**

**Circumvent (n.), the opening in the front of boxer shorts.**

**Coffee (n.), a person who is coughed upon.**

**Esplanade (v.), to attempt an explanation while drunk.**

**Flabbergasted (v.), to be appalled over how much weight you have gained.**

**Frisbeetarianism (n.), the belief that, when you die, your soul goes up  
on the roof and gets stuck there.**

**Gargoyle (n.), an olive oil-flavored mouthwash.**

**Lymph (v.), to walk with a lisp.**

**Negligent (v.), to absentmindedly answer the door in your nightgown.**

**Oyster (n.), a person who sprinkles his conversation with Yiddish expressions.**

**Pokemon (n.), a Carribean proctologist**

**Rectitude (n.), the formal, dignified demeanor of a proctologist .**

**Testicle (n.), a humorous question on an exam.**

**Willy-nilly (adj.), impotent.**

## 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 2002 with the Human Genome Project (HGP), and related genetics/genomics news, provided chronologically:

**Jan 2002** Comparative gene-order studies [*Am J Hum Genet* 2002; **70**: 83] indicate that segmental duplications of DNA [as large as 1 megabase (Mb)] have been an ongoing process of primate genome evolution over the past 35 million years.

We've heard of *BRCA1* and *BRCA2* genes that, when mutated, increase one's risk of breast cancer. Now comes word of a "*BRCA3* gene" on chromosome 13q21. If it turns out to be a susceptibility gene, however, it can only account for a small proportion of non-*BRCA1/2* families having multiple cases of early-onset breast cancer [*PNAS* 2002; **99**: 827].

Why won't investigators give out relevant data or materials promptly, to all scientist colleagues who request them? The biggest problems in delaying the dispersal of information and reagents are the "effort required to produce the materials/information," "need to protect graduate students, postdocs or junior faculty," and "cost and time required to ship chemicals, clones and transgenic mice" [*Science* 2002; **295**: 599].

**Feb 2002** Systematically searching vertebrate mRNA sequences, Lehner et al. [*Trends Genet* 2002; **18**: 63] identified a surprisingly large number of human *anti-sense* transcripts—suggesting that regulation of gene expression by "RNA interference" (RNAi) might be a common phenomenon in mammals. The creation of stable "knock-down" cell lines [*PNAS* 2002; **99**: 1443] should enable researchers to study more extensively the phenomenon of RNAi.

Many have long wondered if pediatric patients, cured of a cancer by radiation therapy, might have children with more risk of birth defects or genetic disorders. The answer appears to be "There is no such risk" [*Am J Hum Genet* 2002; **70**: 1069].

A portion of the rat vanilloid receptor confers sensitivity to *capsaicin* (the hot stuff in chili peppers), but the chicken receptor does not have this segment [*Cell* 2002; **108**: 421]. This explains

why capsaicin offers protection to chili peppers against predatory mammals, whereas birds are indifferent to these pain-inducing effects and therefore serve as vectors for seed dispersal.

It is likely that the "lack of ability to carry a tune" (*amusia*) is similar to "difficulty in reading" (*dyslexia*) in that they are both caused by mutations in one or more genes [*Nature* 2002; **415**: 589].

The first genome from a tree—the poplar (genus *Populus*)—will be completely sequenced by the end of 2003 ([www.jgi.doe.gov](http://www.jgi.doe.gov)). This was chosen first because: it is heavily studied, it grows rapidly so that knowledge of this genus will aid commercial enterprises, and it will help us learn how woody plants evolved. The genome of the first evergreen tree, pine (genus *Pinus*), will be sequenced shortly thereafter.

**Mar 2002** When subjected to severe drought conditions, some organisms enter a state of suspended animation (*anhydrobiosis*). This is a common phenomenon in plants, but the gene for this has now been found in a nematode (worm) that is capable of doing the same thing [*Nature* 2002; **416**: 38].

Bacteria have one set of chromosomes (*monoploid*), and the rest of us have two sets (*diploid*), except some fish (e.g. trout) are *tetraploid*. Now comes word of green toads (*Bufo viridis complex*) in northern Central Asia that have a *triploid genome* and reproduce bisexually [*Nature Genet* 2002; **30**: 325].

Familial adenomatous polyposis coli (APC) predisposes people to colorectal cancer in middle age and is caused by mutations in the *APC* gene. *APC* is the same as the mouse *Min* gene—except it only accounts for ~50% of the trait, suggesting that other genes are modifying *Min*. The first modifier-of-*Min* (*Mom1*) encodes a phospholipase A<sub>2</sub>. The second one (*Mom2*) has been mapped to a Chr 18 region containing the *Smad4* gene, mutations of which in humans are responsible for some cases of juvenile polyposis [*Nature Genet* 2002; **30**: 249].

Human lymphocyte antigen (*HLA*) genes are similar to the major histocompatibility complex (*MHC*) genes that affect rodents' behavior, including nesting and mate choice. Young women were asked to report their preference ("familiarity, intensity, pleasantness and spiciness") of odors derived from males having a wide range of ethnic backgrounds [*Nature Genet* 2002; **30**: 175]. The scientists studied how the women's choices varied with a

limited number of *HLA* alleles. Surprisingly, a woman's preference for odors was not just for *HLA* gene products similar to her own, but for odors that came from individuals having *HLA* gene products most similar to the woman's father...!!

**Apr 2002** The 466-Mb genome of the most widely-cultivated subspecies of rice in China, *indica*, has been sequenced [*Science* 2002; **296**: 79] and is estimated to contain between 46,000 and 56,000 genes. Most of the genome of the *japonica* subspecies of rice has also been sequenced and assembled [*Science* 2002; **296**: 92], with gene numbers predicted in the range of 32,000 to 50,000. The rice and human genomes thus appear to have a comparable number of genes. With such similarity to corn, wheat and barley, *knowledge of the rice genome* should provide a boon to agricultural improvements in many cereal crops [*Nature* 2002; **416**: 590].

The largest cooperative unit (of living organisms) ever recorded is the *Argentine ants* of southern Europe [*PNAS* 2002; **99**: 6075; *Science* 2002; **296**: 653]. This underground ant colony ranged from the Spanish Atlantic Coast more than 6,000 km (~3,700 miles) down into Italy...!!

The familial nature of schizophrenia does not conform to any simple dominant or recessive mode of inheritance. A recent study [*PNAS* 2002; **99**: 3717, 4755] strongly suggests that genetic variation in the *PRODH2* gene (whose product is involved in *transfer of redox potential across the mitochondrial membrane*) is one possible cause of schizophrenia susceptibility. A few other, or perhaps many other genes probably also contribute to this disorder.

The number of genes encoding small RNAs (~22 nucleotides) and that appear to be involved in RNA interference (RNAi) appears to be in the hundreds or thousands [*Cell* 2002; **109**: 137; *Nature Genet* 2002; **30**: 363; *Trends Genet* 2002; **18**: 171]. Bacteria use RNAi in order to respond quickly to environmental changes [*Cell* 2002; **109**: 141].

What are the causes of the U.S. epidemic of obesity and (mature-onset) diabetes type II? Sixteen candidate diabetes genes are discussed in [*Science* 2002; **296**: 686].

Although we are taught that half our genes come from the father and half from the mother, the two parental genomes are not equivalent. It is known that embryos with two male or two female genomes cannot develop normally. There are subtle *epige-*

*netic* forms of regulation (*e.g.* DNA methylation of almost 50 maternal and paternal genes) that are required for successful embryo development [*Science* 2001; **294**: 2536; *Nature* 2002; **416**: 491, 539; *Development* 2002; **129**: 1983].

In humans and other primates, there are 4-6 times more germline mutations in males than females, confirming earlier studies that support the view that DNA replication errors in sperm reflect strong male-driven evolution [*Nature* 2002; **416**: 624; *Nature Genet* 2002; **31**: 9].

A periodic table of chemical elements was developed by Mendeleev more than a century ago. Now, a "periodic table" for protein structures has been proposed [*Nature* 2002; **416**: 657].

**May 2002** A draft sequence of the *C57BL/6J mouse genome* has now been made public by the Mouse Genome Sequencing Consortium [*Nature* 2002; **417**: 106]. The data from this strain will complement the sequence data already available (for a price) from three other inbred strains—129X1/sV, A/J and DBA/2J—reported by Celera in Aug 01.

The forebears of flowering plants appear to have been aquatic weedy herbs [*Science* 2002; **296**: 821, 899].

Empirically derived maps identifying active areas of RNA transcription on human chromosomes 21 and 22 indicate there are ~770 well-characterized and predicted genes [*Science* 2002; **296**: 916].

The European Union of Mouse Research for Public Health and Industrial Applications (EUMORPHIA) had a meeting in Paris of its 17 members. They have decided to standardize the flood of data being generated by studies of mouse mutants [*Nature* 2002; **417**: 211]. More than 600 mutant lines (created by chemical mutagenesis) plus several hundred knockout mouse lines, will be screened at two levels.

The *SLC22A12* gene encodes a transporter protein that reabsorbs uric acid. Patients with uric acid kidney stones have defects in this gene [*Nature* 2002; **417**: 393, 447]. Since uric acid is an antioxidant which theoretically should increase one's life span, would a normal *SLC22A12* gene be more often seen in individuals with increased longevity,

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## ONLY IN AMERICA

is lemon juice made with artificial flavor, and dishwashing liquid made with real lemons!

those who live past 90-100 years?

Hirschsprung (HSCR) disease is the most common cause of intestinal obstruction. Mutations in the *RET*, *EDNRB* and *SOX10* genes (each involved in neural-crest development) appear to account for the *long*-segment form of the disease (L-HSCR). A total-genome scan of 49 S-HSCR families, having the *short*-segment form of this disease, came up with three loci: 19q12 and 3p21 not previously associated with HSCR, plus 10q11 at which *RET* is located. [*Nature Genet* 2002; **31**: 11, 89]. The *multiplicative* model fits their data best—suggesting that these three loci interact to cause S-HSCR.

From evolution-developmental biology (*evo-devo*) studies, it appears that “the eye” might have evolved only one time. It is postulated that the original eye belonged to a microbe that later became a chloroplast (a subcellular organelle used by plants for photosynthesis), and then moved on as the *Pax6* gene to numerous species including sponge, *Planaria* (a flatworm), fruit fly, mouse, and human [*Science* 2002; **296**: 1010].

All genomes are potentially targets of invasion by viruses and transposable elements (“jumping genes”). Could it be that the mechanism of RNA interference (RNAi), with its hundreds or thousands of little genes now being found in many genomes including mammals, is used to combat such invasions [*Science* 2002; **296**: 1263]..?

The genome has a surprisingly structured architecture. There are segments of DNA, called *haplotype blocks*, which can be 1-2 kb or more than 1 Mb in length, that have been inherited from our parents, grandparents, and so on [*Science* 2002; **296**: 1391]. Older populations (*e.g.* African) that have been on this planet longer have shorter blocks (due to more chances at recombination during meiosis to make sperm and ova) than younger populations (*e.g.* Finns). Whether constructing a “HapMap” (a haplotype map of the entire human genome in dozens of the most ethnically diverse populations in the world) will help us in understanding complex diseases—is being fiercely debated.

The National Human Genome Research Institute (NHGRI) announced that the next genomes with highest priority for sequencing include: *chimpanzee*, *honeybee*, *chicken*, *sea urchin*, *the protozoan Tetrahymena thermophila*, and *a fungus* [*Science* 2002; **296**: 1590]. The rhesus macaque monkey came in as #7 in line, with cow and frog (*Xenopus*) still further down the list.

Comparing the mouse and human genomes so far, the mouse has 14 genes with no known human orthologs, whereas the human has 21 genes with no known mouse orthologs. Given the evolutionary point at which the mouse and human species diverged (~90 million years), this computes to about one new gene that has arisen or disappeared every 192,000 years [*Science* 2002; **296**: 1617]. There are more surprises [*Science* 2002; **296**: 1601]. The so-called “*junk*” DNA, long stretches interspersed between genes and sometimes within genes, seems *highly conserved* during the past 90 million years; these might represent regulatory sequences far, far away from the genes they control, or sequences needed for chromosome-pairing (mitosis, seen before cell division). Some noncoding DNA regions have mutated a lot (“genetic drift”), whereas other noncoding regions have remained incredibly constant. The human genome contains 234 “gene-poor” sections ranging in size from 620 kb to 4 Mb and comprising 9% of the genome; 178 of these are in common with the mouse.

Recent studies using reporter-gene constructs [*Genome Res* 2002; **12**: 770] indicate that as much as one-fifth of the 18,959 annotated genes in *Caenorhabditis elegans* (nematode, roundworm) might be nonfunctional (*i.e.* pseudogenes).

**Jun 2002** A portion (15-18%) of the genome of *Caenorhabditis briggsae* is available at <http://genome.wustl.edu/projects/cbriggsae/index.php?blast=1>. Comparison of this small amount from *C. briggsae* to the completed genome of the other worm *Caenorhabditis elegans* [*Genome Res* 2002; **12**: 843] shows 517 chromosomal rearrangements would be needed to explain the data. This suggests that the genomes have had ~4,030 rearrangements since they separated from one another between 50 and 120 million years ago..!!

The recent genome sequences of two related sea squirts, *Ciona savignyi* and *Ciona intestinalis* (simple marine organisms called *tunicates*), are now available [*Science* 2002; **296**: 1792]. Tunicates have little in common with vertebrates; they have no head or tail and live attached to the sea floor. The larvae look a lot like tadpoles. Information from these two *Ciona* species, compared with that in vertebrates, should give evolution-developmental biology (*evo-devo*) researchers more information about how the neural crest and spinal cord develops.

The (*ACE*) gene, encoding angiotensin-converting enzyme ACE, is associated with cardiovascular disease, because high activity leads to angiotensin II formation, which is responsible for blood-vessel constriction and subsequently higher blood pressure. ACE inhibitors are a common form of treatment for people with hypertension. Now comes discovery of the *ACE2* gene, located on the X chromosome. From knockout mouse studies, it appears that it is *the absence* of ACE2 that leads to heart problems [*Nature* 2002; **417**: 822]. ACE is ubiquitous whereas ACE2 is expressed solely in the heart, kidneys and testis. The role of ACE2 on angiotensin II formation remains to be resolved.

## Observations by a Biologist

### Why do some invertebrates have more legs than others?

In issue #17 of *Interface*, we discussed the fact that homeobox (*HOX*) genes *in the developing vertebrae*, regulated by sonic hedgehog (SHH) pathways, do not become activated in snakes, whereas they do in other *vertebrates* that have legs [*Nature* 1999; **399**: 474]. What about with *invertebrates* (animals such as flies or worms *that have no spinal cord*)?

Suppression of abdominal limbs in insects depends on functional changes in a protein called Ultrabithorax (UBX), which is a *Hox* gene product. UBX represses the expression of the *Distalless* (*Dll*) gene—which is required for limb formation (such as in the anterior abdomen of the fruit fly *Drosophila* embryo). In crustaceans (*e.g.* the brine shrimp *Artemia*), however, all of their little developing legs have high levels of UBX; the same is true for the velvet worm (*Onychophora*, close relatives of arthropods), which have legs on all segments. It turns out that the UBX protein in *Drosophila* is structurally different from that in crustaceans and onychophorans [*Nature* 2002; **415**: 848, 910, 914], thereby explaining the difference between fruit flies having six legs on just a few controlled segments and brine shrimp or velvet worms having legs on all segments.

## WORKSHOPS and SPONSORED SPEAKERS

### Dr. Christopher A. Bradfield

Professor of Oncology at the University of Madison  
Thursday, 18 April 2002 “*Dioxin, clocks and oxygen: prototype signals of a nuclear sensor superfamily.*”

### Genomics and Protein Analysis Facilities & Services Core Workshop

22 Jan 02

G Leikauf, S Khan, D Blankenship, P Limbach

### Symposium on "Genomics & Clinical Medicine"

4 Apr 02

sponsored by CEG's Ecogenetics Research Core

G Grabowski, DW Nebert, R Deka, R Chakraborty, L Jin, A Roses, A Menon, S Liggett, M Keddache, J Bezerra, S Miller

### 4th Annual Midwest DNA Repair Symposium, "DNA Double Strand Break Repair"

4-5 May 02

co-sponsored by CEG's Genetic Toxicology Research Core; K Dixon, J Groden, Y Sanchez, MB Kastan

### Conditional Knockout Mice Workshop

17 Jun 02

T Doetschman, J Whitsett, DW Nebert, TP Dalton, J Molkenin

# CEG Members in the News

**Tom Doetschman** chaired an Ad Hoc Review for NRCC on “Rat Genetic Engineering” (Feb 2002), organized a Conditional Knockout Mouse Workshop for Center for Environmental Genetics (Jun 2002), and was awarded a Pilot Project from the NIEHS’ Comparative Mouse Genomics Consortium for designing new targeting strategies for introducing human polymorphisms into mouse genes (Jun 2002).

**Dan Nebert** was recognized for the third time by the Institute for Scientific Information (ISI) as coauthor of a *Citation Classic*<sup>(R)</sup> for the Nelson et al., *Pharmacogenetics* **6**: 1-42 (1996) paper. Citation Classics are published in ISI’s Essential Science Indicators (ESI) on the website <http://www.esi-topics.com>. He was also listed among “The top 0.1% Contemporary Scientists Most-Cited 1981-99,” and from the earlier (1965-78) era, from a compilation of more than 5 million names in all scientific fields by ISI (Philadelphia, Pennsylvania). In addition, Dr. Nebert was an invited speaker in the Symposium on “Genetic Susceptibility to Inhaled Pollutants” at the 22nd Annual Meeting of the Society of Toxicology (Mar 2002, Nashville, Tennessee); at the Symposium on “Applying New Biotechnologies to the Study of Occupational Cancer” sponsored by National Institute of Occupational Safety & Health (NIOSH) (May 2002, Washington, D.C.); at the Symposium on

“Ethnic and Genetic Variation in Response to Occupational Chemicals” in the Third International Conference on Oxygen/Nitrogen Radicals: Cell Injury and Disease,” sponsored by NIOSH (June 2002, Morgantown, West Virginia); and at the Symposium on “Human Genetic Variability” during the 38th Annual Meeting of the Drug Information Association ( Chicago, Illinois, Jun 2002).

**Alvaro Puga** chaired a session at the International Symposium on Cell Signaling, Transcription and Translation as Therapeutic Targets, in Luxembourg, giving a presentation on “*The Ah receptor and cell cycle regulation*” (Jan 2002), and also chaired a session at the 40th Society of Toxicology Annual Meeting in Nashville, Tennessee presenting the talk entitled “*Ah receptor signaling*” (Mar 2002).

**Glenn Talaska** is part of the the Organizing Committee for the NIOSH-sponsored Meeting "Applying Biomarkers to Occupational Health Practice" to be held in Apr 2003.

**Craig Tomlinson** was an invited speaker at the *Neurospora crassa* Conference, Asilomar, CA (Mar 2002) and the Neurofibromatosis conference held in Aspen CO (Jun 2002).

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## Genome Size and Chromosome Number

Evolutionary geneticists are trying to make sense of genome structure, and the data from various species are so highly variable that this makes the task very difficult [*Nature* 2002; **417**: 374].

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	Genome size (bases)	Number of chromosome pairs
<i>Amoeba dubia</i>	670 billion	(several hundred)
Trumpet lily	90 billion	12
Mouse	3.4 billion	20
Human	3.2 billion	23
Carp	1.7 billion	49
Chicken	1.2 billion	39
Housefly	900 million	6
Tomato	655 million	12

Equally problematic is the number of genes versus the presumed complexity of the organism, as has been discussed in previous issues of *Interface*, and also discussed in this issue (for example, it looks like the rice and human genomes have a comparable number of genes)..!

# LETTERS TO THE EDITOR

## RESPONSES/COMMENTS TO VARIOUS QUESTIONS

**Q** I heard something on the radio about a “checkpoint” gene, joining *BRCA1* and *BRCA2* as major genes associated with increased risk of breast cancer. What are they talking about?

**A** A large Breast Cancer Consortium has now identified the *CHEK2* gene, at chromosome 22q12.1, as one of the so-called “low-penetrance” breast cancer susceptibility genes [*Nature Genet* 2002; **31**: 3, 55]. *CHEK2* encodes a cell-cycle checkpoint kinase that is activated in response to DNA damage and prevents the cell from entering mitosis (cell division). A defect in the *CHEK2* gene leads to a 2-fold increased risk in breast cancer in women, and a 10-fold increase in men. So, *BRCA1* and *BRCA2*, combined, are responsible for 5% to 8% of all inherited risk of breast cancer in women, and *CHEK2* offers an additional risk. It is estimated there are another 5 to 10 (or more?) major genes—yet to be identified—contributing to inherited breast cancer risk.

In fact, Ponder and coworkers [*Nature Genet* 2002; **31**: 33] have calculated that, assuming all of the susceptibility genes could be identified, the half of the population at highest risk would still account for 88% of all affected individuals; in contrast, if currently identified risk factors for breast cancer were used to stratify the population, the half of the population at highest risk would account for only 62% of all cases.

**COMMENT** A human embryonal kidney cell line EcR-293 was designed so that *BRCA1* could be induced. Microarray analysis of these cells, with and without high *BRCA1* activity, resulted in the expression of 62 genes altered more than 2-fold. *BRCA1*-regulated genes associated with breast tumorigenesis included the estrogen-responsive *MYC* and cyclin D1 (*CCND1*) genes, *STAT1* and *JAK1* (in the cytokine signaling pathway), laminin 3A (an extracellular matrix protein), *ID4* (an inhibitor of DNA-binding factors), and *STC1* (stanniocalcin, a prohormone lost in breast tumor cells) [*PNAS* 2002; **99**: 7560].

**COMMENT** According to the 2002 edition of *Jobs Rated Almanac*, published by editors of *The Wall Street Journal*, the BEST JOB in the U.S. in terms of low stress, physical safety, high compensation, lots of autonomy, and tremendous hiring demand—among other criteria—is **A BIOLOGIST**. In 2001, the best job “financial planner” was ranked first. Many believe that the terrorist attacks, plus anthrax and chemical warfare fears, are obvious reasons why biologists are now in increased demand [*Nature Genet* 2002; **31**: 131].

⊗⊗⊗⊗ IS A PESSIMIST'S BLOOD TYPE ALWAYS B-NEGATIVE? ⊗⊗⊗⊗

## Ethical, Legal and Social Issues, ...

What follows is a synopsis of some of the more interesting things that have happened during the first 6 months of 2002 with ethical, legal and social issues (ELSI) related to the Human Genome Project, provided chronologically:

**Jan 2002** An American Society of Human Genetics (ASHG) committee of twelve was appointed to examine the widely publicized allegations by journalist P. Tierney (see previous issues of *Interface*) against the recently deceased Professor James V. Neel. The ASHG inquiry found these allegations to be “gross misrepresentations and basically false” [see details in *Am J Hum Genet* 2002; **70**: 1].

**Feb 2002** The Ohio Board of Education introduced a bill, “Intelligent Design,” calling on teachers to “disclose the historical nature” of evolutionary theory and help students understand why “origins science” may generate controversy (doesn’t this sound a little bit like Kansas in late 1999?). Lawmakers eventually stripped the amendment from the bill, but, still, many in the state of Ohio are promoting “intelligent design” and “evidence-against evolution” proposals [*Science* 2002; **295**: 963; *Nature* 2002; **416**: 250].

**Mar 2002** In experiments designed to help people with severe forms of paralysis, a research team at Brown University implanted special electrodes in the brains of rhesus monkeys and taught them to slide an icon around a computer screen just by *willing it* to move [*Nature* 2002; **416**: 141]...!! The ability to move an object simply by thinking (“*telekinesis*”) may help paralyzed humans in the future.

**Apr 2002** Cultured lymphoblastoid cell lines (LCLs), derived from 1,064 individuals of different world populations, have been deposited at the Centre d’Etude du Polymorphisme Humain (CEPH) in Paris. Each LCL is registered in a project-specific database and provided with CEPH identifier numbers and subject information. All were donated under conditions of informed consent and confidentiality. DNAs from this human genome diversity cell panel are available to any investigator, worldwide, who wishes to study any genetic markers and

disease risk in ethnically distinct populations [*Science* 2002; **296**: 261].

According to a poll carried out by the Science Advisory Board of more than 1,000 life scientists, 38% approve of paying for access to genome companies that offer sequence data (*e.g.* Celera), whereas 41% disapprove of the practice and are cheering for the development of comparable tools by government-funded researchers so that access to such sequence data is free [*Nature Genet* 2002; **30**: 355].

A special issue of [*Environ Health Perspect* 2002; **110**:(Suppl 2)] is devoted to advancing *environmental justice* through community-based participatory research with government funded science. Air pollution, and control of house dust and such allergens, are at the top of the list of concerns.

**May 2002** To guard against terrorism, the U.S. Department of Agriculture is no longer permitting foreign scientists or students to work in its labs [*Science* 2002; **296**: 996]. Some members of the National Academy of Sciences claim that this is an overreaction to legitimate concerns about national security [*Nature* 2002; **417**: 105].

In a study of the pre-industrial era (1640-1870) in Northern Scandinavia [*Science* 2002; **296**: 1085], it was found that the more sons delivered to a woman, the shorter her life span. They felt the most likely reason for this finding is that sons are physiologically more demanding—faster intrauterine growth, heavier birth weight, longer time until the mother can reproduce again—than daughters.

In addition to age, sex, diet, underlying disease, and the concomitant use of other medications—race and genetic factors have been shown to sometimes play pivotal roles in the variability of patient response to particular pharmaceutical agents. It is important for NIH and the Food and Drug Administration (FDA) to implement guidelines for the participation of minority groups in clinical trials [*N Engl J Med* 2002; **346**: 1373, 1400].

Want to hear the latest on industry opposing genomic legislation about who has property rights over sequences and DNA variant sites? Check out [*Nature Biotechnol* 2002; **20**: 419].

**Jun 2002** The worldwide occurrences of arsenic in ground water have been nicely reviewed [*Science* 2002; **296**: 2143], with the countries of Bangladesh, West Bengal (India), Vietnam and Thailand as having the most serious problems.

## “Q” Quote of the Month....

"Less than zero? No. I am more than one. I am more than one half my father and half my mother. And more, I am one-fourth of each of all four grandparents. And more, each brother and each sister is half of me - and I am half of them. And all of the people of the world are my brothers and my sisters."

"I am represented in every trait I manifest, and more, I take part in every belief I choose to hold. I am in part each thought, memory and feeling, but yet more than all parts by themselves."

"I am more than one."

"I am my past, my environment, and my free will. I am half nature, half nurture, and more halves adding to more than one."

"Yes, I am more than one."

"I am conscious and unconscious, and more, I am the record of my history, and the fount of history to come. And more, I am the choice, the chooser, and the chosen. I choose this life, and more."

"Yes, I am more than one."

"I am past, present, future, another when, another where. Less than zero. No, I do not admit too less than infinity! Yes, I am more than one, and so are you." *Jonathan Von Post*

### Should Science Be Done by Farmers or Hunter-Gatherers?

NIH is currently weighing the issues involved in a "big science" approach to proteomics. A 5-year plan for identifying all (several hundred thousand) human proteins will be unveiled next spring [*Nature* 2002; **417**: 107].

NIH faces a growing problem in balancing, between funding the large institutes and centers (an analogy would be "large farms"), versus supporting the individual laboratory ("hunter-gatherer"). The NIH budget will have doubled in 2003 [*Science* 2002; **296**: 1401] from the budget in 1998, but (although the average funding per grant has increased 44%) there will be actually fewer R01 (individual) grants in 2003 than in 2002.

Many believe that the major innovative, creative research has almost always been generated by the individual investigator—rather than large Centers and Consortia that support the administrative infrastructure of universities, medical centers, and research institutes.



If swimming is good  
for your shape, then  
why do the whales  
look the way they do?



## Really Kewl Web Sites

This site provides continuously updated information on both ongoing and completed sequencing projects—of which there are presently **656** in total...!! Also useful links to taxonomic information on each organism.

<http://wit.integratedgenomics.com/GOLD/>

This site is a web dictionary for the International Union of Pure and Applied Chemistry (IUPAC). If you want to know what arachidonic acid is, or the various retinoids, or bile acids, check here.

[www.chemsoc.org/chembytes/goldbook](http://www.chemsoc.org/chembytes/goldbook)

The fly people name their *Drosophila* genes just about anything: *fear-of-intimacy*, *son-of-seven*, *drop-dead*, *mothers-against-drunk-drivers*, *barbie*. Why not tap into this site to understand what the relationship is between these genes and the genes of all other organisms?

<http://www.flynome.com/>

If you want the names and structures of several hundred pharmaceutical chemicals—from aspirin to Prozac, check this one out, from Tokyo University of Pharmacy.

<http://triton.ps.toyaku.ac.jp/~dobashi/database/english/index.html>

PicSNP, a database from the University of Tokyo, has tried to simplify the job of finding single-nucleotide polymorphisms (SNPs) of possible significance. Of 1.2 million SNPs catalogues, the curator has found ~3800 that change the amino acid sequence of proteins.

<http://plaza.umin.ac.jp/~hchang/picsnp/>

For the latest on asthma and which genes might cause this disorder, check out this site from Munich, Germany:

<http://cooke.gsf.de/asthmagen/main.cfm>

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## Pilot Project Recipients 2002

The Center for Environmental Genetics Year 11 Pilot Projects have been awarded. **CONGRATULATIONS** to the awardees!

**Mary Beth Genter**, Department of Environmental Health: "**Genetic factors contributing to alachlor carcinogenesis.**"

**Jonathan Bernstein**, Department of Internal Medicine: "**Genetics of nonallergic vasomotor rhinitis.**"

**Nira Ben-Jonathan**, Department of Cell Biology, Neurobiology and Anatomy: "**Xeno-estrogens and differential pituitary gene expression profiles in estrogen-sensitive and estrogen-insensitive rat strains.**"

**Scott M. Belcher**, Department of Pharmacology and Cell Biophysics: "**Proteomic analysis of differential estrogen sensitivity in developing neurons.**"

**Zalfa Abdel-Malek**, Department of Dermatology: "**Loss-of-function mutations in the melanocortin-1 receptor gene sensitize melanocytes to the photo-damaging effects of UV radiation.**"

**Gary Dean**, Department of Molecular Genetics: "**Worms and bacteria as environmental tools.**"

**Bandana Chakraborty**, Department of Environmental Health: "**Effects of lead exposure and genes on postural balance.**"

**Susan Pinney**, Department of Environmental Health: "**Population representative case: control series for an association study of Parkinson disease.**"