



INTERFACE: GENES AND THE ENVIRONMENT

CENTER FOR ENVIRONMENTAL GENETICS UNIVERSITY OF CINCINNATI SUMMER/FALL 2002

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Memoir of a Mostly Research Career in Environmental Health

by Roy E. Albert MD

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Roy E. Albert, MD, scientist, died of pancreatic cancer on March 25, 2002. Dr. Albert was born in New York City, Jan 11, 1924, and graduated from NYU's School of Medicine. While at NYU, where he became vice chairman of the Department of Environmental Medicine, he worked on lung clearance and tumorigenesis. Dr. Albert wrote a portion of the Surgeon General's Report on Smoking. He also served as the director of the Department of Environmental Health at the University of Cincinnati, from 1985-94, and PI (1985-1991) for our NIEHS Environmental Health Sciences Center. Later he was Professor Emeritus. In his scientific career in cancer research, which spanned more than 50 years, he published more than 200 papers. Dr. Albert was an elected Fellow of the American Association for the Advancement of Science. He received the Stockinger

Award, as well as several medals from the EPA for developing the field of carcinogen risk assessment. Dr. Albert remained active in later years, attaining his pilot's license after age 70. He played the violin in the Seven Hills Sinfonietta, was an avid tennis player, and participated in the Senior Olympics. Some of the flavor of his life can be felt in his memoirs, as well as a glimpse of the dire working conditions and the unhealthy labor practices he saw. What follows is the beginning of his memoirs. The entire document can be accessed at <http://eh.uc.edu/ceg/albertsmemoirs.pdf>

Preface

For several decades immediately after World War II, federal research budgets increased exponentially every year. If one had reasonable ideas, it was possible to get funding. It permitted somebody like me, who was trained in a relatively unspecialized way as an MD, to do research in a variety of fields. To write these memoirs is one way of describing a checkered career.

I have told stories about my research experiences to people in various stages of post-prandial torpor. My wife, Abby, insisted that I write them down, presumably so she wouldn't have to listen to me telling them anymore. I do so, in more or less sequential order, sticking to the facts as I remember them. I hope that the facts don't differ too much from the recollections of those involved at the time.

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Chapter 1. Sweating at Fort Knox

I was in medical school in 1943 at New York University (NYU), when we got put into the Armed Services Technical Program. The medical students continued on as before, except there were no summer vacations. Since I started medical school after the third year at Columbia (I miss that fourth year to this day), which I entered at age 16, I was a ripe old 22 when my MD was awarded. Abby and I were married when we were both aged 21, so I was somewhat grown up.

I had two research experiences in medical school. The first was when I walked the halls outside of Milton Levy's lab in the Chemistry Department. I was trying to get up enough nerve to go in to ask him to let me work on an idea. I thought that a mixture of ionized chemicals could be separated in an electrical field. This is conventional now, but had not been discovered then. I did not get up the courage and that is why I never became a biochemist.

The second research experience was in Albert Keston's laboratory. He was the model of a "mad" scientist: wildly enthusiastic, bubbling with ideas, gulping handfuls of thyroid tablets, and waxing lyrically about pastrami sandwiches. He talked so fast that I couldn't understand what he was doing. It was something about acetylcholine, and he used leech muscles because of their exquisite sensitivity to acetylcholine. He sent me down to the bowery to restock his supply of leeches from some really old-time pharmacy stores that were down there at the time. When I told him that I was getting married, he said, "I'll never see you again." He was right.

The military took over the medical schools, because they wanted to ensure a supply of doctors. Probably as a payback for not being put in the infantry, they required 2 years of military service after internship. I took my internship in Internal Medicine at the Bellevue Third Medical Division, which was run by NYU. We were then assigned to Fort Sam Houston in Texas for orientation. The only thing I learned there was how to grade beef.

When asked, I told the Army that I wanted to do research, so they assigned me to the Third Amored Division Research Laboratory at Fort Knox, Kentucky. That laboratory was set up because of the high incidence of heat stroke among tank crews fighting in the North African desert. The Army had assembled a bunch of academic stars at the lab—including Norton Nelson, Ed Palmes, Rollo Park, Bill Ashe, Tony Lanza, Bill Machle, Ludwig Eichana, and Ted Hatch. All went on to distinguished academic careers afterwards. They literally invented thermoregulatory physiology in humans and developed a rational way to prevent heat stroke. It was an early example of combining physiology and engineering to produce a new field of research.

When I arrived, all of the stars except Ed Palmes had left for universities. So, I worked with him and Herman Schachner, another MD serving his 2 years. The lab I worked in was a "hot room," big enough to hold a military tank (minus the cannon), and equipped with machinery that could regulate the temperature up to 120° F and control the humidity to whatever level one wanted. Ed Palmes had just finished an experiment with Rollo Park on the

thermoregulatory changes in humans when developing fever. They gave each other, and volunteer GI subjects, an i.v. shot of typhoid vaccine (ugh!).

The subject lay nude inside a coffin-like box, on a webbed cot with Saint-Saens third piano concerto banging in his ears. Thermocouples were strapped onto the skin at various spots. There was a recording rectal thermometer, a rig to measure oxygen metabolism, and a set-up to measure the amount of sweat the subject produced. Dry air was pumped into the box and flowed over the subject, evaporating the sweat. The moisture-laden air then went out through another pipe, to an infra-red gas analyzer that measured the water-vapor content in the air. The more sweating, the higher the water vapor-content, so a continuous record of sweating was obtained. Ed and Rollo were struck by the fact that the sweating from their subjects, as measured by the water-vapor content of the air leaving the box, was not constant and they wondered why.

It seemed to be a good idea to look at sweating, using this same method, but from a small skin area. I don't remember whether this was my idea or Ed's. I think it was Ed's. He was prone to come up with something so simple and elegant that it was a genius of an idea. For example, he thought of a way to sample gases in the atmosphere that required only an open tube with one end closed, and coated with an absorber at the bottom closed end. The gases would be picked up in the absorber, and the amount analyzed after a collection period. The rate of sampling was determined by the length and diameter of the tube. No power was needed to run the sampler. It could be worn on a lapel. There are international meetings now that are being held to discuss new applications of Ed's idea.

Ed also did a notable science project for one of his kids. It was common for fathers to do the science project for their children in those days; I also did one. Ed's was a stand that held a metal ball, that fell on a holder on which was placed a cookie, thereby breaking the cookie into pieces. There were a series of sieves of graded hole sizes under the biscuit, that captured the fragments and thereby permitted them to be counted according to size. The title of the project was, "How the Cookie Crumbles."

So, we made a small cup that was shaped like a stovepipe hat, but not so tall. It had a tube in the side near the brim, and another tube coming out of the top of the cup. The opening of the cup was about 2 inches across. The open face of the cup was applied to the skin. Again, dry air entered the cup and evaporated the sweat on the surface of the skin, and the moisture-laden air exited the cup and went through the infra-red water-vapor analyzer. The

water-vapor content was continuously monitored, by a pen held against the moving paper of a strip-chart recorder. The higher the deflection for the pen, the greater the water-vapor concentration, *i.e.* the more sweating, and the constancy of the sweating, was indicated by the degree of flatness of the tracing.

We were astonished to see that the line drawn by the pen was anything but flat. It went up and down continuously, which suggested that the sweating from the skin was not constant—for reasons unknown. At that point, Ed Palms left to go to NYU, where he joined Nelson and Lanza in the Department of Industrial Medicine. This is the Department I also joined in 1959. Herman Schachner was out of the picture, because he shot himself, not long after I arrived at Fort Knox. He was a German-Jewish refugee who was chronically depressed. He had a Teutonic need to control things. He tried to do that with a horse that had thrown him, and was kicked in the face as a result. This caused a depressed fracture of the cheek bone that displaced an eye. That was the last straw for his depression. There went a fine person and a bright academic career. In any case, I was left alone with the sweat study, because Ed and Herman were gone.

Everybody loves simple experiments that open new worlds. Like the old Greek observation of adding salt to a full cup of water, without its overflowing, demonstrating that apparently solid matter is full of holes. Then there was the one by Otto Loewe, the Nobel prize winner, who gave us a lecture in medical school. He discovered something he called, in his thick Prussian accent, “Vagus-shtuff.” He told us how he woke up one night with a great idea but, to his horror, forgot it in the morning. In desperation, he put a pencil and paper at his bedside, in case the idea came back to him at night. Sure enough several nights later, he awoke with the same idea and wrote it down. This was his idea: he put a beating turtle heart with its attached vagus nerve in a beaker of saline. He stimulated the vagus nerve electrically, and the expected slowing of the turtle heart occurred. Then he discarded the slowed turtle heart, and put a fresh beating turtle heart with its attached vagus nerve in the same beaker that had held the first turtle heart. (Lo (Loewe)) and behold, it slowed down like the electrically stimulated heart, but without any stimulation of the vagus nerve. Some substance had gotten into the beaker of saline, when

he stimulated the heart. He discovered that nerves, when stimulated, produce their effects by releasing the chemical, acetylcholine. With that experiment, he revolutionized neurophysiology.

I never did a revolutionary experiment that got me a Nobel prize, but I did an inspired thing with the sweating experiment. I went over to the stockroom and got another infra-red water-vapor analyzer. Amazingly enough, they had one on the shelf. I duplicated the initial set-up, including a second cup just like the first one. In short, I had two identical set-ups for measuring sweating, and I got a strip-chart recorder that had two pens—one for each sweat-measuring set-up. I had the hot room turned up to about 110 degrees F, so that I was sweating briskly. I then put one cup on my forehead and the other on the front of my chest. Lo and behold, the two pens on the strip-chart recorder went up and down as if they were tied together! No matter where I placed the cups on different parts of skin, the same thing happened. I had discovered that sweating occurs in squirts, synchronously over the surface of the body.

The next question was whether there was something inherent in sweat glands that made them function intermittently, or whether it was the nervous system that made them discharge periodically. It was known that sweat glands are under control of the autonomic nervous system, which are two strings of nerve cells that lie along each side of the spinal column, discovered by the great Walter Cannon of Harvard. This system controls the body's vegetative functions, such as digestion and sweating, as well as keying up the body for emergencies by releasing adrenaline, the “fight-or-flight” response. Cannon gave a series of lectures at the NYU medical school. People were hanging from the rafters at his first lecture. But he was so dull, that there were only a

few die-hards in the audience at the end of the series. He had a bad case of radiation dermatitis, because he had used unshielded x-ray tubes in his studies of the nervous control of the GI tract. So, he just scratched and mumbled. I can't remember anything he said. It was like being there when Jesus gave his Sermon on the Mount, but you couldn't hear a word because he just scratched and mumbled.

If your interest has been piqued, check out the rest online!





Voodoo Science

Check out Robert L. Park's book, "Voodoo Science: The Road From Foolishness to Fraud" (Oxford University Press, 2002).

The National Aeronautics and Space Administration is investing close to a million dollars in an obscure Russian scientist's anti-gravity machine, although it has failed every test and would violate the most fundamental laws of nature. NIH is investing millions in repeated analyses of the negligible effect of electromagnetic force on human health. The Patent and Trademark Office recently issued Patent 6,362,718 for a physically impossible motionless electromagnetic generator, which is supposed to snatch free energy from a vacuum. Moreover, major power companies have sunk tens of millions of dollars into a scheme to produce energy by putting hydrogen atoms into a state below their ground state, a feat equivalent to mounting an expedition to explore the region south of the South Pole.

Park has identified seven indicators that a scientific claim lies well outside the bounds of rational scientific discourse. Of course, they are only warning signs—even a claim with several of the signs could be legitimate. [1] The discoverer pitches the claim directly to the media. [2] The discoverer says that a powerful establishment is trying to suppress his/her work. [3] The scientific effect involved is always at the very limit of detection. [4] Evidence for a discovery is anecdotal. [5] The discoverer says a belief is credible because it has endured for centuries. [6] The discoverer has worked in isolation. [7] The discoverer must propose new laws of nature to explain an observation. In our increasingly technological society, spotting voodoo science is a skill that every citizen should develop. See also <http://chronicle.com/free/v49/i21/21b02001.htm>

Are part-time band leaders semi-conductors?

webb-cytes

If you want to know the size of any organism's genome, check out: www.genomesize.com

If you want to know where a particular gene is turned on during different stages of development of the fruit fly, as well as DNA microarray expression profiles, see: www.fruitfly.org/cgi-bin/ex/insitu.pl

Measuring the activity of hundreds, or even thousands, of genes is now routine—using microarrays (gene chips). Colleagues at the University of Lund (Sweden) have designed BASE, database software that you can download for free, make your own modifications, and share any improvements through this web site:

<http://base.thep.lu.se>

If you wish to know more about regulators, policymakers, and academics of agricultural science—including a list of more than 1400 papers on biosafety and genetically modified (GM) organisms, check out: www.agbios.com

You can find items to give your brain a workout, provocative essays that explore logic or display exemplary reasoning, and discussions of science versus dubious pseudoscience at: www.philosophy.unimelb.edu.au/reason/critical/index.htm

You can download many free medium- and high-resolution photographs of vertebrates, invertebrates, plants and landscapes (mostly from North America) from this U.S. Fish & Wildlife Service site:

<http://images.fws.gov>

The *Interface* keeps chatting about that nematode, *Caenorhabditis elegans*, research on which led to the 2002 Nobel Prize. An anatomical atlas of this tiny round-worm, with no eyes or heart and only 959 cells, can be found at: www.wormatlas.org

The *Interface* also continues to have articles about the latest in human origins. To keep up on this subject, check out: <http://www.nature.com/nature/ancestor>

The U.S. Geological Survey has links to more than 40 Webcams that are continuing to watch active volcanos around the world. Spectacular fire fountains, flowing lava, spewing ash, and tremors can be seen at:

http://vulcan.wr.usgs.gov/Photo/volcano_cams.html

The network of Mutant Mouse Regional Resource Centers (MMRRC) was established to accept mutant mice from donating investigators for the purpose of transferring the lines to requesting investigators or institutions. These genetically modified lines include models for studies, for example, of cardiovascular disease, cancer, diabetes, obesity and epilepsy:

<http://www.mmrrc.org/index.html>

Observations by a Biologist

What determines the social status of the honeybee?

For 15 years, Maria Sokolowski (behavioral geneticist at the University of Toronto) has tried to track down the gene that makes some fruit flies more lazy than others. In the so-called "sitter flies," she reported in *Science* in 1997 that the *For* gene (named for foraging activity) was less active than it is in their high-energy neighbors that don't sit still.

In the lab of Gene Robinson (entomologist at University of Illinois, Urbana-Champaign) the honeybee version of the *For* gene was isolated and checked for activity in the brains of both the stay-at-home drones and the food-gatherer workers. They found that the *For* gene was indeed more active in the forager bees, similar to what was found in the wide-roaming fruit flies. The gene was then found to encode *cyclic GMP-dependent protein kinase* (PKG), which is involved in cell signaling. Since there are activator chemicals known for stimulating PKG activity, they treated the lazy bees with this activator and caused the activity of the drones to be as high as that of the workers [*Science* 2002; **296**: 636, 741]. Other chemicals that inhibited, or had no effect on, the PKG had no effect on the honeybee's activity.

In the fire ant (*Solenopsis invicta*), a single allelic difference at the *Gp9* locus specifies the number of queens a colony has, and, thus, controls the social structure of the colony [*Science* 2002; **295**: 328]. The gene product GP9 encodes a pheromone-binding protein implicated in chemical recognition of nestmates—consistent with workers determining their queen number as a function of the workers' plus the queens' *Gp9* genotypes.

It seems hard to believe that a single gene can affect the social behavior of insects so dramatically. In issue #7 of *Interface* we had noted that differences in physical activity, translated from wheel-running activity, suggested that a mouse gene for "couch potato" might exist. It remains to be seen whether it might be that simple in humans, *i.e.* for tired or lazy (teenagers? or adults?) having the defective *FOR* gene to administer this PKG activator in order to get them motivated. Certainly, just giving them coffee to drink is not enough for some people...!!

“Q”
Quote of the month...The trick
is to grow up without getting old”

.....Frank Lloyd Wright 1867-1959

New Society Created to Promote the Study of Disease-Causing Gene Variations

In November 2001, the Human Genome Variation Society (HGVS) was founded. Professor **Richard Cotton** of the Genomic Disorders Research Centre, Melbourne, a world leader in human genome variation detection, was appointed President of the new society. Other world-renowned medical geneticists, including Victor McKusick of Johns Hopkins University, Baltimore, Maryland, and Charles Scriver of McGill University, Montreal, Canada, were elected to its Board of Directors. See the new organization's Web site at www.hgvs.org “Scientific journals have stopped publishing reports of single-gene variations after the first five or ten,” Cotton said. “Also, diagnostic laboratories often are too busy to report disease-causing variations in their patients, so that others may benefit from their experience. Around the world, we have groups of very dedicated scientists creating databases for their own use. This situation is a major obstacle to effective health care today. What's needed is a central repository and coordination of collection of all this information.”

One of the most dramatic findings from the study of the human genome has been that specific genes can be faulty in hundreds, or even thousands, of ways, Cotton said. “This means that if we have 30,000 genes and each one can be faulty in hundreds of ways, we could have up to tens of millions of ways of causing human disease.” He said a group of the HGVS members will work with the many experts in particular gene/gene families and central bioinformatics facilities around the world to set up a system to document and deliver variation data. After review, these data are to be stored and made freely available on the HGVS's online database. Some data passing stringent review may be published by special arrangement with the society's official research journal, *Human Mutation* [published by Wiley-Liss, Inc., New York].

The HGVS grew out of the Human Genome Organization (HUGO) Mutation Database Initiative (MDI), which was generously supported by grants from the March of Dimes Birth Defects Foundation (White Plains, New York), and substantial assistance has been from HUGO based in London. The mission of the **Human Genome Variation Society** [whose founders' list includes **Dan Nebert** of the University of Cincinnati] is to enhance human health through identification and characterization of changes in the genome that lead to susceptibility to illness. To this end, it will collate the genomic information necessary for molecular diagnosis, research on basic mechanisms, and design of treatments of human ailments.

Ethical, Legal and Social Issues....

Tidbits from the last 6 months of 2002:

Jul 2002 An epidemiologic perspective on the issue of “human categorization in biomedical and genetic research” strongly supports the continued use of self-identified race and ethnicity, says Risch and coworkers [*Genome Biol* 2002; **3**: 2007.1]. This report was directed at other recent reports [*N Engl J Med* 2001; **344**: 1392; *Nat Genet* 2001; **29**: 239 & 265;] for suggesting that race or ethnicity is “biologically meaningless.” Risch’s article set off a small firestorm in the scientific community [*Nature* 2002; **418**: 355; *Science* 2002; **298**: 1337]. It is the view of this Editor (DWN) that Risch is speaking from the view of a statistician or epidemiologist (studying a population of 1,000 or 100,000 subjects), whereas the others are speaking from the point of a physician—where *individualized therapy* (regardless of racial or ethnic outward appearance) for the patient is what is ultimately the most important.

A high-resolution recombination map of the human genome is needed, before we can begin to understand *haplotype blocks*. The most current standard, the Marshfield map, was based on only 188 meioses; this has now been superceded by Kong et al. [*Nat Genet* 2002; **31**: 1 & 241], who have genotyped 5,136 microsatellite markers for 146 families—all from **Iceland**—arriving at a total of 1,257 meiotic events. Maternal recombination rates appear to be affected by both genetic and environmental factors.

A “rational view of insurance and genetic discrimination” was presented [*Science* 2002; **297**: 195]. What is the meaning of life insurance and the threat of genetic discrimination by life insurers? Should life insurers be allowed to order genetic tests?

A U.S. government study on hormone replacement therapy (HRT) in women over 50 was reported to cause almost a 2-fold rise in blood clots, plus small increases in heart attack, stroke and breast cancer. While this news stunned the nation, it was not much appreciated that HRT significantly decreased the risk of hip fractures and colorectal cancer [*Science* 2002; **297**: 326].

Thirteen scholars from 12 universities independently reviewed the historical and DNA evidence and unanimously found the paternity of the slave Sally Hemings’ descendants could suggest no specific male of the Jefferson family; contrary to continued claims in the press [*Nature* 2002; **417**: 213], therefore, the paternity by Thomas Jefferson “is by no means proven” [*Nature* 2002; **418**: 125].

Aug 2002 The consumer’s **Charter for Genomic Services** [*Nat Biotechnol* 2002; **20**: 767] includes [a] provision of information, [b] direct access to testing, [c] personal control of the information, [d] reassessment of regulations, and [e] generation of data to guide the consumer’s choice. Forensic DNA testing should be done either on everyone, or no one [*Nature* 2002; **418**: 585].

Oct 2002 The World Intellectual Property Organization (WIPO) wants to establish databases in which indigenous populations would record their cultural knowledge [*Nature* 2002; **419**: 866]. At the World’s Indigenous People’s conference held this month in British Columbia, however, some groups were concerned that the databases could be used to exploit their cultural heritage.

Smokebush has been used to develop an anti-AIDS drug by an Australian-based pharmaceutical company. The Nyoongahs have used smokebush for thousands of years. A conference in New Caledonia (South Pacific Island) agreed upon a model law that would ensure that indigenous communities involved in such drug discovery are properly rewarded [*Nature* 2002; **419**: 423].

Ohio is the next Kansas, as far as the board of education trying hard to push through a course of “Intelligent Design,” a concept favored by creationists, to be taught as high-school “science” [*Science* 2002; **298**: 739]. It was finally decided that the teachers “could elect” to discuss this topic but that students will not be tested on it.

Nov 2002 Almost 20 years ago, Amerindians on Vancouver Island (Canada) who agreed to donate blood were told the genetics research would be only on rheumatoid arthritis—a disease rampant in their tribe [*Nature* 2002; **420**: 111]. The DNA samples were transported by Ryk Ward from the University of British Columbia to the University of Utah in 1986 and then to University of Oxford, U.K. in 1996, as he changed jobs, and the DNA has been used for numerous medical genetics studies. Leaders of the Nootka tribe have complained of their DNA being exploited. International rules are needed to ensure that human biological samples are respected. [*Ed. Note—We are very saddened to hear, as this Interface issue goes to press, that our colleague and friend Ryk Ward died suddenly on 14 Feb 2003 of a heart attack at age 58.*]

The International Nucleotide Sequence Database has a uniform policy of free and unrestricted access to all information in the database, there can be no statements attached to restrict access to these data,

the information will remain permanently accessible and fully disclosed to the public, and the quality and accuracy of the submitted data are the responsibility of the submitting author, not INSD [*Science* 2002; **298**: 1333]. Many are complaining that they have generated the data, only to have others jump in and "mine" the data before the original researchers can do so [*Science* 2002; **298**: 1312].

Countries and health providers are following Iceland's (and the deCODE company's) path in combining health and genetic data on large populations [*Science* 2002; **298**: 1158]. There is a promise to deliver "personalized medicine," but many have doubts about how easy this might be.

Dec 2002 Canada's highest court denied Harvard's request to patent the "onco-mouse" in that country [*Nature* 2002; **420**: 593], saying that a "higher life form is not patentable because it is not a 'manufacture' or 'composition of matter'." The court did not, however, rule out Harvard's claims on the process used to make the onco-mouse.

Cadmium is a toxic heavy metal that can cause kidney and liver toxicity as well as certain types of cancer. People are exposed to cadmium via cigarette smoke, ingestion of contaminated fish or shellfish, and ingestion of plants grown in contaminated soil. Cadmium consumption was not correlated with urinary or blood cadmium levels [*Environ Health Perspect* 2002; **110**: A764], underscoring the likelihood that human genetic factors are important in cadmium-induced toxicity and/or cancer.

CEG Members in the News

Tom Doetschman was awarded a Pilot Project from the NIEHS' Comparative Mouse Genomics Consortium for designing new targeting strategies for introducing human polymorphisms into mouse genes (Jul 02).

Grace LeMasters was appointed to the Federal Advisory Committee for NICHD for the National Children's Study and also the Armed Forces Epidemiology Board.

MaryBeth Genter was invited to make a "fast-breaking research talk" at the Mechanisms of Toxicity, Gordon Conference (Bates College, Lewiston, ME, Jul 02).

THOUGHT FOR THE DAY.

* * * * * * * * * * * * * * * * *
If it is true that more money is being spent on breast implants and Viagra than on Alzheimer's research, by 2020 there should be a large elderly population with perky breasts and erections and no recollection of what to do with them.
* * * * * * * * * * * * * * *

Dan Nebert gave the overview to begin the Symposium on "Role of Cytochromes P450 in Proliferation, Differentiation, and Apoptosis," at the 14th International Union of Pharmacology (IUPHAR) Congress of Toxicology in San Francisco, CA (Jul 02) and was Keynote Speaker at the First Scientific Symposium of the Comparative Mouse Genomics Centers Consortium (CMGCC) in Seattle, WA (Aug 02) and the Plenary Session, "Human Genome: the Aftermath and the Future," at the Annual Meeting of the North American International Society for the Study of Xenobiotics (ISSX) in Orlando, FL (Oct 02). He was also an invited speaker at the 14th International Symposium on "Microsomes and Drug Oxidations" in Sapporo, Japan (Jul 02), and gave workshop and symposium lectures at the Annual Meeting of the American Association of Pharmaceutical Scientists (AAPS) in Toronto, Canada (Nov 02).

Alvaro Puga was chosen to be Chairperson of the Alcohol and Toxicology-1 NIH Study Section for a 2-year period starting July 1, 2003.

Peter Stambrook is Chair of the NIEHS Comparative Mouse Genome Centers Consortium, Chair of the Israel Cancer Research Fund Scientific Review Panel, and Internation Scientific Council Editor-in-Chief (for the Americas) of *Mutation Research: Fundamental and Molecular Mechanisms*.

Nancy Warren was awarded a University Faculty Research Grant on the Research Values and Practices of Genetic Counselors.

"great men are not always wise"

Biotechnology, ...

Tidbits from the last 6 months of 2002 on genetically-modified (GM) plants, biotechnology.

Jul 2002 At a conference in New Delhi, India, it was generally agreed that developing countries would embrace genetically-modified organisms (GMO; plants, animals) if they had a mechanism in their countries to ensure that GMO introduction is safe to their people and to the environment [Nature Biotechnol 2002; **20**: 641]. Africa has rejected all GM food aid, which represents principally a chasm of misunderstanding that is only made worse by exaggerated claims for the benefits of the technology [Nature 2002; **418**: 569 & 571].

Although cut roses bring in profits of ~US\$10 billion worldwide, the flowers often smell mostly like the wax paper wrapping. Now, scientists are using genomics and classical biochemistry to restore scents to flowers that have been bred for their appearance and long vase life [Science 2002; **296**: 2327]. Genes being used include those encoding for the cytochrome P450 (CYP) enzymes, well-known in animals for metabolizing drugs and carcinogens.

At high concentrations, caffeine is a lethal neurotoxin for slugs and snails. Moreover, caffeine is far safer than pesticides and insecticides on plants [Nature 2002; **417**: 915].

Drug giants and biotech companies increasingly turn to collaborations with start-up companies. “Merger medicine” does not seem to be working. Merged companies are still facing the same problems as smaller companies [Nature 2002; **418**: 353].

There are expected to be ~6 million common (frequency of 0.10 or higher) single-nucleotide polymorphisms (SNPs) worldwide. How many of these DNA variant sites across the genome will be needed for detecting all common *haplotypes* (pattern of SNPs on a single chromosome) is a question being feverishly studied. Allen Roses proposes that a *genetic profile* of each individual can be used to identify patterns of susceptibility (to some disease, or to a drug), such that the knowledge of the genes involved (or of the mechanism that causes the trait) need not necessarily be known [Nat Reviews 2002; **1**: 541].

Aug 2002 Nuclear-transfer cloning of intact zebrafish and medaka fish [Nat Biotechnol 2002; **20**: 785 & 795; PNAS 2001; **98**: 1071] now joins the ranks of other intact animals (sheeps, cows, pigs and mice) in being successful. In cloned mice, however, defects at the DNA level have been detected in at least 4% of the genes examined [PNAS 2002; **99**: 12889].

Environmental concerns about the impact of GM animals on natural ecosystems [Nature 2002; **418**: 805] are at the top of the list of scientific concerns by a panel convened by the U.S. National Academy of Sciences and the Food and Drug Administration (FDA).

Sep 2002 A consortium, headed by the International Plant Genetic Resources Institute (Rome), delivered wheat seed to 70,000 farmers in 11 provinces of Afghanistan last spring, but the amount of looting and especially vandalism has mostly destroyed this humanitarian effort [Nature 2002; **419**: 103].

Biology teachers in high schools and universities need to build up their courses in the areas of computer science, mathematics and physical sciences [Nature 2002; **419**: 102]. There is an explosion in the need for experts in genomics and bio-informatics.

DNA expression data are notoriously variable, as discussed in previous issues of *Interface*. The international Microarray Gene Expression Data (MGED) group has now proposed a checklist of variables and controls for DNA chip experiments [Nat Genet 2002; **29**: 365], also online at http://www.mged.org/Workshops/MIAME/miame_checklist.html

New information is being made available to rice researchers and farmers. The Rice Knowledge Bank, based in the Philippines [www.knowledgebank.Irri.org], and microarrays containing 54,000 predicted genes from the Beijing Genomics Institute [Science 2002; **296**: 79], are being offered free to the public.

Between August 2000 and August 2002, stocks have gone down by 83% to 95% in biotech companies such as Celera Genomics, CuraGen, Genset, Human Genome Sciences Inc., Hyseq Pharmaceuticals Inc., Incyte Genomics Inc., Lexicon Genetics Inc., Millennium Pharmaceuticals Inc., Myriad Pharmaceuticals Inc. and SEQUENOM [Science 2002; **297**: 1982].

Oct 2002 A viral-mediated delivery mechanism for supplying small interfering RNA (siRNA) to cells in culture as well as to intact animals has been described [Nat Biotechnol 2002; **20**: 1006]. This technique may have very important ramifications to gene-expression research, as well as possible human therapy! A systematic **RNAi** screen of 5,690 *C. elegans* genes [Nat Genet 2003; **33**: 40] is an example of how RNA interference will help us understand gene-expression pathways.

Imai et al. [Nature 2002; **419**: 685] showed that it might be possible to make a genetically-modified onion, by suppressing synthesis of propanthial S-oxide

(which causes tears to anyone cutting up onions) while promoting formation of thiosulfinate (responsible for the flavor of fresh onion; also having fat-lowering and anti-clotting effects).

Concern about GM foods has been summarized [*Nat Biotechnol* 2002; **20**: 969]. Basically, a foreign gene harmless to humans when made in bacteria might be modified by plants to something harmful, might evoke the synthesis of carcinogenic/toxic/teratogenic or allergenic chemicals in the plant, or might lead to synthesis of unexpected endogenous products that interfere with normal cellular pathways in the plant.

What are the top ten biotechnologies for improving health in developing countries? A panel of 28 experts [*Nat Genet* 2002; **32**: 229] ranked the importance of these as:

1. Need for simple affordable diagnosis of infectious diseases
2. Recombinant technology to develop vaccines against infectious diseases
3. More efficient drug and vaccine delivery systems
4. Environmental improvement (sanitation, clean water, bioremediation)
5. Sequencing genomes of pathogens to understand their biology and identify new antimicrobials
6. Female-controlled protection against sexually transmitted diseases (with, and without contraception)
7. Bio-informatics to identify drug targets and pathogen-host interactions
8. Genetically-modified crops with increased nutrients to counter specific deficiencies
9. Recombinant technology to make therapeutic products (e.g. insulin, interferons) more affordable
10. Combinatorial chemistry for drug discovery

Nov 2002 The government of Zambia surprisingly rejected a donation of thousands of tons of corn donated by the U.S. because it is likely to be contaminated with some GM kernels [*Science* 2002; **298**: 1153]. Their refusal to accept this donation leaves an estimated 2.9 million people at risk of starvation.

Dec 2002 The Alliance for Cellular Signaling [*Nature* 2002; **420**: 703, 708 & 712] is a large-scale collaboration designed to answer questions about signaling networks. This approach is similar to what has been called by Lee Hood “Systems Biology” and by NIEHS “Systems Toxicology.”

The research collaboration between Syngenta (based in Switzerland) and several research groups in India, involving more than 19,000 unique local strains of rice, appears on the verge of breaking down [*Nature* 2002; **420**: 596].

Human Gene Variability.....

Tidbits from the last 6 months of 2002 concerning our realization of how variable the human genome is.

Aug 2002 Since 1995 it has been known that mutations in a sodium channel gene, *SCN5A*, can cause “long-QT syndrome,” a rare hereditary heart rhythm disturbance (so named because of a particular change in patients’ electrocardiograms). Another *SCN5A* mutation, almost exclusively found in Africans, is associated with an increased risk of arrhythmia caused by certain antihistamines and drugs used to treat high blood pressure [*Science* 2002; **297**: 1333].

Sep 2002 A new book—*Where do we come from? The molecular evidence for human descent* by J Klein and N Takahata (Springer; Berlin/Heidelberg/New York), 2002, 462 pages—has received glowing reviews. Highly recommended for college/university students studying genetics [*Hum Genet* 2002; **111**: 579].

Oct 2002 Looking at the expression of 907 genes within the same population of 15 teleost fish (northern plus southern *Fundulus heteroclitus*, plus *F. grandis*, five each), Oleksiak and coworkers found significant differences (1.5- to sometimes more than 2-fold) in 18% of the genes [*Nat Genet* 2002; **32**: 261]. As Darwin proposed, quantitative variation is central to evolution of any species. There is no reason to believe that the same sort of thing will not be seen in human or wild mouse populations !

Nov 2002 The 3-year US\$100-million **HapMap Project** has now been launched by a U.S.- and Japanese-led global consortium. This project plans to chart genetic variation across the entire human genome [*Nature* 2002; **419**: 870; *Science* 2002; **298**: 941].

Venter (formerly of Celera) now has plans to sequence the complete genomes of 1,000 individuals of diverse racial and ethnic backgrounds [*Science* 2002; **298**: 947].

Latest in Genetics and Genomics, ...

Jul 2002 In past *Interface* issues we have discussed the Mouse Genome Database (MGD), with genomes of three inbred strains (129X1/Sv, A/J and DBA/2J) from Celera and of one strain (C57BL/6J) from the Mouse Genome Sequencing Consortium [*Mamm Genome* 2002; **13**: 481]. For single-nucleotide polymorphisms (SNPs), the inbred strains being covered include:

Celera Mouse SNP Strains	
Mouse Strains in dbSNP	129X1/SvJ
129X1/SvJ	C57BL/6J
129S1/SvlmJ	129S1/SvlmJ
A/J	A/J
AKR/J	CAB/J
BALB/cByJ	DBA/2J
C3H/HeJ	K1
SPRET/Ei	129S1/SvlmJ
SWR/J	BALB/cJ
	C3H/HeJ
Whitehead Institute Genome Project	

Some have questioned the success of quantitative trait locus (QTL) mapping in isolating and actually identifying genes. A list of 29 QTL genes (human, mouse, rat, pig), with almost half identified during 2001, shows that this approach is indeed becoming highly fruitful [*Nat Genet* 2002; **31**: 235].

Aug 2002 Gene duplications have been a major cause of increasing a genome's number of functional genes during evolution and of speciation [*Science* 2002; **297**: 945]. The average duplication rate is ~1% per gene per million years. Comparison of the human and mouse genomes indicate a larger than expected number of rearrangements, some of megabase (Mb) size and others of much smaller (hundreds and thousands of bases) size; more rearrangements have occurred within a chromosome than between chromosomes [*Genome Res* 2003; **13**: 37].

The sequence of most of the pufferfish (*Fugu rubripes*) genome has been completed [*Science* 2002; **297**: 1301]. These data allow us to begin to understand what has happened during the 450 million years, since teleost fish and mammals (human, mouse) diverged during evolution. A preliminary assembly of the zebrafish (*Danio rerio*) genome was also released this month.

www.ensembl.org/Danio_rerio

A physical map of the mouse genome, containing 296 contigs (overlapping bacterial clones) and almost 17,000 unique markers, has now been reported [*Nature* 2002; **418**: 743].

Sept 2002 The protozoan *Oxytricha trifallax*, the cow and the dog genomes are newcomers—joining the chicken, chimpanzee, honeybee, sea urchin, the protozoan *Tetrahymena thermophila*, and 15 species of fungi [*Nat Genet* 2002; **32**: 225]—on the high-priority list for sequencing by the U.S. National Human Genome Research Institute (Bethesda, MD). *Oxytricha* is an evolutionary oddity in that it seems to package each of its ~30,000 genes into one tiny individual chromosome, thus having a similar number of genes as the mouse but a genome ~60 times smaller [*Nature* 2002; **419**: 237].

Oct 2002 Comparing the human and chimpanzee genomes, several groups suggest that the two might not be as identical (98.5%) as previously thought [*Science* 2002; **298**: 719]. Five chimpanzee bacterial artificial chromosome (BAC) sequences were compared with the best matching regions of the human genome sequence: ~95% of the base pairs are exactly shared in this sample of 779 kb, divergence due to base substitution is 1.4%, and there is an additional 3.4% difference due to the presence of insertions and deletions [*PNAS* 2002; **99**: 13633].

Nov 2002 The complete sequences of rice chromosomes 1 and 4 have been described [*Nature* 2002; **420**: 259, 312 & 316]. A draft version earlier this year predicted the existence of only 4,467 genes, whereas the calculations are now that this chromosome 1 contains 6,756—a 51% increase in number. There seems to be little conservation in gene order between rice and *Arabidopsis thaliana* (the tiny mustard plant whose genome had been previously sequenced).

Once a government agency is formed, the rule is that it can never decrease in size or be eliminated. Such is the case with the National Human Genome Research Institute (NHGRI). The most controversial part of the draft plan for NHGRI's future (after sequencing the genomes of chimpanzee, rat, cow and about 20 other mammals, fungi and protozoa) involves suggestions that they dabble in clinical medicine [*Science* 2002; **298**: 1694].

Tsetse flies (the vectors of African trypanosomes, agents of deadly diseases in humans and animals in sub-Saharan Africa) harbor a symbiotic microbe, *Wigglesworthia glossinidia*, in gut tissue. The fly feeds exclusively on blood and relies on this intracellular microbe for nutrition and fecundity. This co-evolution of insect and microbe results in the loss

of the symbiont's ability to survive outside the host insect cells. The complete sequence of the microbe's genome (one chromosome of 698 kb plus one plasmid of 5.2 kb) surprisingly bears hallmarks of both parasitic and free-living microbes [Nat Genet 2002; 32: 402].

Dec 2002 The Mammalian Gene Collection Program Team reported the generation of more than 15,000 full-length human and mouse cDNA sequences [PNAS 2002; 99: 16899].

The first chordates appeared in the fossil record at the time of the Cambrian explosion—nearly 550 million years ago. The chordates subsequently diverged into three subphyla: urochordates (tunicates), cephalochordates, and vertebrates (see **Figure 1**). It is generally believed that the *urochordate* lineage is the most basal among chordates, and the *ascidians* (common name: sea squirt) are the most prevalent modern urochordates. The *Ciona* branch on the evolutionary tree puts it closer to humans than other invertebrates such as the nematode and fruit fly, but, of course, much farther away from humans than mice. The *Ciona intestinalis* genome contains ~16,000 protein-coding genes [Science 2002; 298: 2157], which include genes involved in cell signaling and development similar to those found in basic ancestors as well as genes engaged in cellulose metabolism related to those found in bacteria and fungi. The genome of *Ciona savignyi* is also almost completely sequenced. Thyroid hormones and receptors are found in *Ciona*, and of course, humans and mice, but not in worms or flies.

Although most vertebrates increase in size through cell proliferation, some invertebrates exploit

an increase in cell size; larger cells, however, require larger nuclei and perhaps greater ploidy. Humans are diploid (2C), meaning all chromosomes exist in pairs. The marine chordate *Oikopleura dioica*, during its various times of development and life cycle, shows differences in its ploidy ranging from **34C** to **1300C** [Dev Biol 2002; 252: 59]!

A “second-generation gene annotation” of human chromosome 22 [Genome Res 2003; 13: 27] increased the total length in exons by 74% over the previously published annotation. By extrapolation, Collins and coworkers estimate the entire human genome will contain 29,000 to 36,000 protein-coding genes, 21,300 pseudogenes, and 1,500 small interfering RNA (siRNA) “minigenes.”

best TYPO 2002...."Cincinnasti"

INCIDENCE OF DIABETES IN MEXICO AND IN SAN ANTONIO

Speaking about the gene-environment interactions affecting one's health, Burke and coworkers [Diabetes Care 2001; 24: 1573] found that the change in lifestyle of Mexicans, once they move from Mexico City to Texas, dramatically(!) alters the incidence of diabetes mellitus type 2. Whether it is from eating more fatty foods, or less exercise, or a combination of both, both male and female Mexican-Americans show 2- to 4-fold increases in the incidence of diabetes.

Table — Incidence of Type 2 diabetes (per 100 person-years) in 6–8 years of follow-up of Mexico City residents and of San Antonio Mexican-Americans

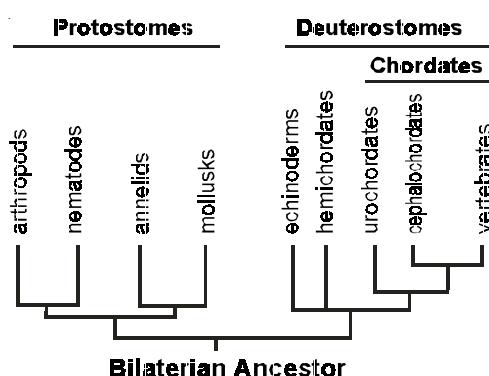


Fig. 1. Phylogeny of bilaterian animals. Humans, mice and fish are vertebrates. The sea squirt is a urochordate.

Age at baseline (years)	Men		Women		<i>P</i>
	Mexico City	San Antonio	Mexico City	San Antonio	
35-44	1.15	1.48	0.660	1.13	1.77 0.220
45-54	1.98	1.93	0.960	1.46	2.77 0.037
55-64	1.07	4.35	0.002	0.96	4.15 <0.001
Total	1.42	2.70	0.008	1.21	2.86 <0.001

Dijon vu ---- same mustard as before

SCIENCE LITE SCIENCE LITE

New Medications for Women

Damitol--Take 2 and the rest of the world can go to hell for up to 8 hours.

St. MomsWort--Treats mom's depression by rendering preschoolers unconscious for up to six hours.

EmptyNestrogen--Highly effective suppository that eliminates melancholy by enhancing the memory of how awful they were as teenagers and how you couldn't wait till they moved out.

Peptobimbo--Liquid silicone for single women. Two full cups swallowed before an evening out increase breast size, decrease intelligence, and improve flirting.

Dumerol--When taken with Peptobimbo, can cause dangerously low I.Q. causing enjoyment of country western music.

Flipitor--Increases life expectancy of commuters by controlling road rage and the urge to flip off other drivers.

Menicillin--Potent antiboyotic for older women. Increases resistance to such lines as, "You make me want to be a better person ... can we get naked now?"

Buyagra--Injectable stimulant taken prior to shopping. Increases potency and duration of spending spree.

Extra Strength Buy-One-all--When combined with Buyagra, can cause an indiscriminate buying frenzy so severe the victim may even come home with a Donnie Osmond CD or a book by Dr. Laura.

JackAsspirin--Relieves headache caused by a man who can't remember your birthday, anniversary or phone number.

Anti-talksident--A spray carried in a purse or wallet to be used on anyone too eager to share their life stories with total strangers.

Sexcedrin--More effective than Excedrin in treating the, "Not now, dear, I have a headache," syndrome.

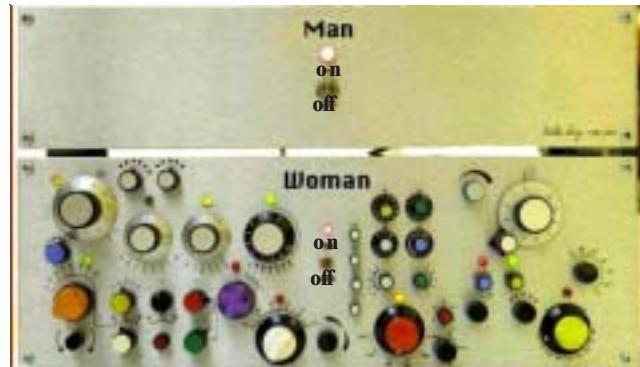
Ragamet--When administered to a husband, provides the same irritation as ragging on him all weekend, saving the wife the time and trouble of doing it herself.

Antiboyotics--When administered to teenage girls, is highly effective in improving grades, freeing up phone lines, and reducing money spent on make-up.

Science ? Lite

Lead cups were used to drink ale or whiskey. The combination of lead and alcohol would sometimes knock imbibers out for a couple of days. Someone walking along the roadside would often take them for dead, and prepare them for burial. The presumed "deceased" were laid out on the kitchen table for a couple of days and families would gather around, and eat, drink and wait to see if the party would wake up, thus began the custom of holding a "wake."

LIFE EXPLAINED!!!



LETTERS TO THE EDITOR

RESPONSES/COMMENTS TO VARIOUS QUESTIONS

Q Did you hear that *Interface* was quoted on National Public Radio's "The 90-second Naturalist?" Thayne Maynard led off with "your" question: if swimming is good for you, then why do whales look as they do? He then went on to talk about sleek cold-blooded fish and plumper warm-blooded whales, and ended by saying that whales were pretty quick for their size!

A Uh, ummm... I guess being quoted on NPR is better than not being quoted.

COMMENT I just want you to know how much *Interface* has helped me in understanding genetics and "omics." I have often referred back to the issues for information that I need as an editor. My background is in English, and the science I've acquired has been through 30 years of editing, so a publication such as yours is a gem for people like me. Especially with the new fields in genomics. I just wanted you to know that your time and effort are appreciated.

COMMENT I always look forward to reading the next issue of *Interface*. Usually I take it on long airplane trips and read it thoroughly, cover-to-cover. Although I like to think that I am up-to-date on every conceivable gene-environment topic, I am always surprised and continue to be amazed to read new things in your NewsLetter that I've never heard about, or that I've somehow missed!

Q I heard something about nitroglycerin on the radio, a new big breakthrough in understanding how it works, but did not catch the details. Might you know what this was about?

A Yes, nitroglycerin (glyceryl trinitrate, GTN), originally synthesized by Alfred Nobel more than 130 years ago and used as an explosive, was also found to effectively treat angina and heart failure. The molecular mechanism of GTN metabolism and action on the heart, however, has remained a mystery. Chen et al. [PNAS 2002; 99: 8306] purified a nitrate reductase that specifically catalyzes the formation of 1,2-glyceryl dinitrate and nitrite from GTN and found that this enzyme led to the production of cGMP and relaxation of vascular smooth muscle. The nitrite is an obligate intermediate in generation of nitric oxide (NO) bioactivity! Even more incredible, this reductase turned out to be mitochondrial aldehyde dehydrogenase (ALDH2). The *ALDH2* gene is known to be defective (by a mutation causing a particular amino-acid change) in 20% to 45% of Asians, but no defect is seen in Africans or Caucasians. ALDH2 deficiency is associated with the "alcohol flushing syndrome," which causes a red face moments after sipping small amounts of alcohol; not surprisingly, then, persons with ALDH2 deficiency rarely, if ever, become alcoholics. Data from the Chen et al. publication would therefore suggest that a high percentage of therapeutic failure of nitroglycerin in treating heart disease would probably go hand-in-hand with the high percentage of ALDH2 deficiency in Asians but not Blacks or Whites.

Graduate students say the darndest things

Words created by grad students during presentations and written on exams

toxicity
hypothamarus
endogenur
craw talks
neurotoxical

hippocameras
hypothalamia
arfa (alpha)
exhibit
extrapt

Gene-Environment interactions....

Tidbits from the last 6 months of 2002

Jul 2002 (or earlier) The possible pathways of detoxification and metabolic activation of arsenic were discussed in issue 13 of *Interface*. It now appears that methylated forms of arsenic may be more toxic than arsenic itself [*Environ Health Perspect* 2002; **110**: 729], which is just the reverse of what was thought back then, in 1998. In addition, a purine nucleoside phosphorylase appears to be an enzyme that fortuitously reduces pentavalent arsenic [As⁵⁺, As(V)], to the trivalent form [As³⁺, As(III)], which shows much higher reactivity with cellular thiols [*Toxicol Sci* 2002; **70**: 1].

The subject of asthma and genetics was first discussed in issue 6 (1995) of *Interface*. In studies of 460 Caucasian families in which at least two siblings were diagnosed as asthmatic [*Nature* 2002; **418**: 426], the *ADAM33* gene (coding for a metalloprotease, which perhaps processes proteins in fibroblasts or smooth-muscle cells) was identified by several genetic approaches. This is not the whole story, but it is at least a start, in understanding this complex disease.

Primary microcephaly is an autosomal recessive neurodevelopmental condition in which the patient exhibits a global decrease in cerebral cortex volume (similar to the size seen in apes). By positional cloning, Jackson et al. [*Am J Hum Genet* 2002; **71**: 136] identified the *MCPH1* gene, the first of six (*MCPH1,2,3,4,5,6*) genes associated with this trait and all discovered over a period of a couple months! Another gene associated with microcephaly is *ASPM*, related to a fruit fly gene that affects the mitotic spindle in neuronal progenitor cells [*Nat Genet* 2002; **32**: 316].

The best genes for longevity are the ones you inherit from your parents if they live to be very old. Male siblings of centenarians are at least 17 times, female siblings at least eight times, as likely to attain the age of 100 themselves [*PNAS* 2002; **99**: 8442].

Aug 2002 Coincidental to our leading article entitled, "Multiple chemical sensitivities syndrome" in issue 22 (2001) of *Interface*, a conference "Environmental factors in medically unexplained physical symptoms and related syndromes" was held in January 2001 in Piscataway, New Jersey, which was summarized in *Environ Health Perspect* 2002; **110/Suppl 4**: 591].

Hydrocarbons in fuels and solvents were shown to affect preovulatory luteinizing hormone [*Environ Health Perspect* 2002; **110**: 805], which suggests they might be endocrine disruptors. Toluene was the most common hydrocarbon found.

Sept 2002 Why does the defective *LKB1* gene in Peutz-Jeghers syndrome patients cause intestinal polyps that seldom go on to become cancer? Studies in the *Lkb1(-/-)* knockout mouse [*Nature* 2002; **419**: 162] showed that LKB1 deficiency is a double-edged sword—somehow promoting perpetual cell growth but preventing malignant transformation.

For the first time it was shown that *Atm(+/-)* mice, having one defective ataxia telangiectasia allele, have a higher risk of radiation-induced cancer, providing further support that human *ATM(+/-)* carriers (which represent ~4% of the population) might also have increased cancer predisposition [*Nat Genet* 2002; **32**: 185].

The last several issues of *Interface* have articles about small temporal (stRNA), small interfering (siRNA), and micro-RNA (miRNAs) as being involved in *RNA interference*. This subject is undoubtedly the hottest, most commonly reviewed subject of 2002. Hundreds of these RNAs (21-28 nt in length) exist in the genomes of many, if not all, species and are involved in the control of translation, RNA cleavage, and genome rearrangement [*Science* 2002; **297**: 2003; *Nature* 2002; **419**: 890].

Oct 2002 Each year we consume ~120 billion aspirin tablets(!), in addition to many other non-steroid anti-inflammatory drugs (NSAIDs), which block inflammation, fever and blood-clotting via PTGS1 and PTGS2 (commonly mistakenly called COX1 & COX2). Understanding this pathway led to the Nobel Prize in 1970 and in 1982. Acetaminophen (Tylenol®) and other anti-pain anti-fever drugs seemed to operate on some other target, however. Now, it's been discovered [*PNAS* 2002; **99**: 13926] that *PTGS3*, a splice variant of PTGS1, is selectively inhibited by acetaminophen and other NSAIDs [*Nature* 2002; **420**: 135].

Speaking of acetaminophen, high doses can cause acute liver failure. Using *Car(-/-)* knockout mice having a disruption in the constitutive androstane receptor gene, Moore and coworkers [*Science* 2002; **298**: 422] showed that inducers of CYP1A2, CYP2E1 and CYP3A (enzymes that metabolically activate acetaminophen) did not cause rises in this enzyme—because CAR is involved in the up-regulation of these genes—and that these mice were extremely resistant to high doses of acetaminophen.

Many of the past *Interface* issues have had articles describing an unknown environmental agent(s) that is/are deforming and killing wild frogs in the U.S. Atrazine, the most commonly used herbicide in the U.S. and probably in the world, now appears to be the culprit and is an endocrine disruptor [*Nature* 2002; **419**: 895]. Later in the year, however, some

groups say they've been unable to reproduce this purported effect of atrazine on frogs [*Science* 2002; **298**: 938].

Exposing one nostril to various odors leads to a learning process in the brain that shares information to the other (unexposed nostril), effectively doubling one's detection accuracy [*Nature* 2002; **419**: 802].

We're sure that Bob Horvitz's parents used to ask him "When are you going to become a *real* doctor, instead of doing research on worms?" Well, the 2002 Nobel Prize in Physiology or Medicine was awarded to Horvitz (MIT), John Sulston (Cambridge, UK) and Sydney Brenner (Salk Institute, San Diego) for their work on growth and programmed death (apoptosis) in the nematode, a roundworm ~1 mm long, called *Caenorhabditis elegans* (*Nature* 2002; **419**: 548; *Science* 2002; **298**: 526).

A report [*The Analyst* 2002; **127**: 880] that many fried and oven-cooked foods cause the formation of acrylamide, a probable human carcinogen, raised public concerns. The mechanism of acrylamide formation is the result of the Maillard reaction between amino acids and reducing sugars [*Nature* 2002; **419**: 449, 450].

Mutations in the interferon regulatory factor-6 (*IRF6*) gene were shown to be the cause of (at least some) cleft lip and/or palate birth defects (van der Woude syndrome) as well as webbing of the skin (popliteal pterygium syndrome) [*Nat Genet* 2002; **32**: 219].

Nov 2002 In an earlier study of 185 Tanzanian children and then a 5-year study of 1106 children in Kenya [*Lancet* 2002; **360**: 1468], it was found that a mutation in the nitric oxide synthase (*NOS2*) gene decreased by almost 90% the risk that malaria will become life-threatening. The exact mechanism of this protective effect is not yet understood.

It is well known that mutations and, hence, inactivation of the *TP53* gene predisposes to cancer, but the opposite may also be true: having more functional *TP53* might help prevent cancer [*EMBO J* 2002; **21**: 6225].

There are estimates in humans that the mutation rate in males is ~5 times greater than that in females [*Nature* 2002; **416**: 624], presumably because ova are the product of relatively few rounds of replication whereas sperm are the result of many more. Looking at spontaneous cases of dwarfism as a function of paternal age, Tiemann-Boege and coworkers did not find increases in mutation as the age of fathers increases [*PNAS* 2002; **99**: 14952]. It is becoming increasingly clear, however, that mutation rates—as well as rates of evolution—vary quite remarkably in different parts of the chromosome.

Termites, leafcutter ants, and beetles have all, independently, learned how to cultivate fungus for

food; the fungus, in turn, grows on the insect feces [*PNAS* 2002; **99**: 15247]. DNA studies on the various species of insects, and their specialized fungus in each case, show co-evolution over 50 million years or longer.

The anti-cholesterol drug, *atorvastatin*, used to treat atherosclerosis and coronary artery disease, was found to be effective against experimental autoimmune encephalomyelitis (EAE), a mouse model of human multiple sclerosis [*Nature* 2002; **420**: 78]. Since statins have already been used to block tissue transplant rejection by the immune system, a relationship between anti-cholesterol drugs and anti-inflammatory events in the central nervous system does make some sense.

Sometimes Mother Nature has tapped the same gene to do very different things. For example, mutations in the *ARX* gene are responsible for both development of the forebrain and the testis [*Nat Genet* 2002; **32**: 359 & 341]!

Dec 2002 Clusters of co-expressed nonhomologous genes implies their co-regulation. A total of 1,661 testis-specific genes, one-third of which are clustered, in the fruit fly [*Nature* 2002; **420**: 666] suggest that transcriptional co-regulation (a "gene battery") occurs much more frequently than previously thought.

In issue 8 of *Interface*, we described the sheep callipyge muscle hypertrophy phenotype ("nice buns"), the only known case of paternal polar overdominance gene action. A likely candidate (*CLPG*) gene has now been identified in sheep, cattle, mouse and human [*Genome Res* 2002; **12**: 1496].

You'd think that one gene and one enzyme would be enough to synthesize serotonin. However, a second tryptophan hydroxylase (*TPH2*) gene has been discovered—in mouse, rat, human and perhaps zebrafish [*Science* 2003; **299**: 76].

**Life is not
measured by the
number of breaths we take,
but by the number of moments
that take our breath
away.**

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

Non-Profit Org
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Permit No. 133
Cincinnati OH

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Research Core Sponsored Speakers and Workshops

The Signal Transduction Research Core sponsored a Workshop on 17 Sep 2002. The Workshop provided CEG members with an overview of the research conducted by the Core members and promoted ideas for future collaboration among center members. Speakers included Puga, Belcher, Ben-Jonathan, Eric and Karen Knudsen, Xia, and Singleton.

A Luncheon, sponsored by the Genetic Epidemiology and Biostatistics F&S Core and the Biomonitoring and Imaging F&S Core, was given on 6 Nov 2002. The main focus of this meeting was to present the services offered by the two Cores and to investigate the needs of CEG members and Pilot Project awardees. Speakers included Talaska, LeMasters, Pinney and Miller.

A Bioinformatics Workshop was held on 12 Nov 2002. The main focus of this Workshop was on microarray experimental design and statistical analysis, applying it to actual experiments designed by CEG members. Speakers included Aronow, Medvedovic and Leikauf.

Narayan Avadhani, Professor and Chair at the University of Pennsylvania, Philadelphia

Friday, 15 November 2002

"Subcellular localization of cytochromes P450: a novel posttranslational processing endopeptidase targets proteins to endoplasmic reticulum or mitochondria."

Welcome, new members

Bing Su, Assistant Professor, Department of Environmental Health. Su joined the Human Populations Research Core in August 2002 as Jr. Investigator. Su's research focuses on primate comparative genomics and human population genetics.

Two new members have joined the Signal Transduction Core: **Scott M Belcher**, an assistant professor in the Department of Pharmacology and Cell Biophysics, with an interest in neural effects of estrogens and endocrine disruptors and **Karen Knudsen**, an assistant professor in the Department of Cell Biology, Neurobiology and Anatomy, whose main interest is in androgen responses in cell cycle regulation and gene expression.