Issue Number 16

NTERFACE: GENES AND THE ENVIRONMENT

CENTER FOR ENVIRONMENTAL GENETICS UNIVERSITY OF CINCINNATI WINTER 1998-99

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Summary of the Regional Town Meeting and Symposium ------- (Cincinnati, Ohio, 19-20 January 1999)

"Environmental Health in Our Neighborhoods: Speaking Out about Pollution and Health"

The National Institute of Environmental Health Sciences (NIEHS) has begun to coordinate regional town meetings and symposia in the locality of each of the more than 25 NIEHS-funded Centers around the U.S.—for the purpose of encouraging interactions among diverse segments of the population. These events help bring new insight to the attending federal government officials as to how the local community is dealing with problems in environmental health. Our regional town meeting and symposium, the third in this series, was arranged by the NIEHS, the University of Cincinnati [the Center for Environmental Genetics (CEG), the Department of Environmental Health and the Superfund Basic Research Program], and the Society of Toxicology. The event was held in the Reakirt Auditorium at the Cincinnati Museum Center. The meeting drew significant participation from members of local and regional community groups, health professionals, government officials, university professors, and the public-at-large. What follows is a brief summary.

IN THIS ISSUE

Regional Town Meeting on Tuesday Evening

The Town Meeting, with an attendance of more than 300, started off with a poster session. There were 31 posters and table exhibits provided by community action and environmental advocacy groups, state and local health and environmental health agencies, labor-related organizations, and faculty from the University of Cincinnati and other nearby colleges and universities.

The purposes of the meeting were to provide a forum for open discussion about the environmental health concerns of people living in the Greater Cincinnati area and to consider ways that community-based organizations, university-based researchers, and other interested groups might work together to address local environmental health issues.

Dr. Marshall Anderson (Chair, UC Department of Environmental Health) welcomed the attendees to the Town Meeting.

Dr. Kenneth Olden (Director, NIEHS) gave an overview of his Institute and the kind of research carried out there. He commented that the NIEHS was sponsoring a series of Town Meetings throughout the country as a means of hearing the public's concerns regarding local and regional environmental health problems.

The Honorable Roxanne Qualls (Mayor of Cincinnati) was the moderator of the Town Meeting. Community leaders who have expertise in dealing with local environmental pollution and human health problems gave brief presentations and facilitated the discussion with attendees.

Mr. David Altman (community environmental lawyer) spoke about the advantages of using environmental legislation to address environmental problems. He also pointed out the importance of taking into account residents' knowledge and first-hand experience of their community.

Ms. Linda Briscoe (community leader) described the hazards created by large landfills and polluting industries near Winton Hills and Winton Place. She suggested that scientists and regulators would benefit from listening to the real-life experiences and "common sense" analyses that

she and her neighbors use in order to address the multitude of environmental problems in their community.

Ms. Pauletta Hansel (community leader) spoke about the barriers with which communities and large institutions must deal before effective collaborations can develop. These barriers include failure to identify and address basic differences in skills, knowledge, approach, language, priorities, and vested interests. She talked about her work with the Lower Price Hill Environmental Leadership Coalition and commented that successful community-based programs require change and growth among all participating organizations and institutions, and not just among the local residents.

Dr. Jim Lockey (Professor, UC Division of Occupational Medicine) described Cincinnati's Environmental Advisory Council, a volunteer organization that advises City Council and the city administration about current environmental issues. He revealed that the council is now studying several different local issues, including the Mill Creek Restoration Plan, the City's waste management plan, and ways to combat environmental lead contamination.

Ms. Edwa Yocum (community leader) spoke about her community's efforts to address the human health effects and environmental pollution in the area around a former federal nuclear weapons plant, referred to as "Fernald," which is located 20 miles northwest of Cincinnati. The organization FRESH (Fernald Residents for Environmental Safety and Health) was formed in 1985 when residential water wells were determined to be contaminated with uranium. Members of FRESH created a map depicting the incidence of cancer among residents living in the vicinity of the plant. Some time later, the Centers for Disease Control and Prevention (CDC) and the Agency for Toxic Substances and Disease Registry (ATSDR) became involved in researching health problems in the Fernald area.

Concerns posed at the Town Meeting

After the presentations by community leaders, attendees at the Town Meeting expressed their concerns. Their comments can be summarized as follows—How can we know to what we are being exposed, in our communities, and to what extent? How many of the illnesses that we are experiencing are brought about by environmental pollutants? Must we present proof that the health problems that we have are related to such exposures? And, if so, how can scientists assist us with these investigations?

Attendees mentioned several areas in and around Cincinnati that have major pollution problems. These include the landfills adjacent to Winton Hills/Winton Place, the contamination of Mill Creek, and potential leaching into the public water supply from an old waste site in Clermont County. There were also specific complaints by residents from the cities of Marion and Columbus, where there are environmental health hazards involving exposures to complex mixtures in landfills and waste sites.

The attendees also brought up their frustration and anger regarding the lack of official response to their repeated complaints about these local environmental hazards. Several people mentioned that the scientific community also seemed to be unresponsive. One person made a plea for substantial campaign reform—that as long as industry lobbyists are allowed to make big contributions to elections, citizens' concerns about the environment will not be acted upon by legislators. Another issue heard was that poor people and racial minorities are more likely to live near landfills and dumpsites (the movement afoot to resolve this problem has been termed "environmental justice").

Dr. Ken Olden (NIEHS) responded to these comments by the Town Meeting attendees by describing relevant work being carried out at his Institute or being funded by his Institute. He commented on how the NIEHS is developing methods to quickly identify many different compounds present in toxic waste dump sites, and how the Institute supports local efforts—through events like this Town Meeting, as well as by financing environmental justice studies.

Regional Symposium, All Day Wednesday: "Preventing and Treating Environmental Health Diseases"

The next morning, **Dr. John Hutton (**Dean, UC College of Medicine) welcomed approximately 180 people to the Regional Symposium.

Dr. Ken Olden (NIEHS) addressed the audience concerning the goals of the NIEHS in 1999 and beyond. The top NIEHS priorities include studies involving differences in individual susceptibilities to hazardous substances, high-tech alternatives to animal bioassays for rapid toxicological testing, characterization of health effects from exposure to complex chemical mixtures, and measuring children's susceptibility and exposure to environmental agents.

Dr. Daniel Nebert (Professor, UC Department of Environmental Health) then reviewed some basic principles of genetics and emphasized the diversity of human genetic make-up and the role of individual susceptibility in the development of environmental diseases. He also gave several examples of individual and population differences in response to therapeutic drugs and toxic chemicals.

In a panel discussion on ***"Asthma and Respiratory Diseases,"*** **Dr. David Bernstein (**Professor, UC Division of Immunology) spoke about patient care and research on allergic asthma. He described the growing asthma problem and likely causes, which include tobacco smoke, cockroach detritus and droppings, viruses, air pollutants, occupational chemicals, toxic irritants, and the underlying genetic susceptibility of the individual.

Dr. George Leikauf (Professor, UC Department of Environmental Health) discussed the role of air pollutants

as a cause of airway disease—including asthma—as well as the genetic basis of increased susceptibility to air pollutants. He pointed out that asthma cases are on the increase in Ohio and in many other parts of the U.S.

An **asthma parent representative** spoke of the ongoing medical care and the daily routines that she and her husband were required to perform, on behalf of their elementary-school-aged twins who both have asthma.

Dr. Ned Ford (Sierra Club) described some major pollution problems in the region. He stated that the societal costs of not cleaning up the sources of air pollution are often higher than the costs involved in curing the diseases that result from them. He emphasized that many of the alternative production technologies are cleaner and more cost-effective than many of those now being used.

In the second panel discussion, entitled ***"Lead-Related Disease,"*** **Dr. Kim Dietrich** (Professor, UC Department of Environmental Health) talked about what is considered to be a clinically significant lead exposure in children. He explained how lead exposures create many health problems for children, including nervous system disorders and mental retardation.

Ms. Marcheta Gillam (Legal Aid Society of Cincinnati) told of her work representing local families that have sought legal advice and court counsel—in dealing with problems related to sources of residential lead.

Dr. Robert Bornschein (Professor, UC Department of Environmental Health) talked about UC collaborations with other local agencies and institutions in local lead abatement programs. He explained how environmental lead contamination occurs when there is scraping or air blasting of walls of old houses having lead-based paint, and also through normal deterioration of painted surfaces.

A **parent representative** described the hardships that she and her young family are facing for having recently purchased and occupied a home that has significant lead contamination. She noted that her two pre-school-aged children have had significant lead exposure and may be at risk for long-term health problems as a result.

The final Symposium panel discussion was entitled ***"Environmental Genetics: Ethical, Legal and Social Issues."*** **Dr. Jeffrey Whitsett (**Professor, Children's Hospital Medical Center) described the high prevalence of serious respiratory disease in pediatric practice. He talked about how genetic research is leading to new therapeutic treatments that hold much promise for preventing and curing many common diseases.

Dr. Gayle Debord (National Institute of Occupational Health and Safety) outlined the sources of genetic information, including genetic screening to determine one's underlying predisposition, genetic monitoring to determine exposure to environmental agents, and medical records. She said that some important issues have emerged regarding the misuse of genetic information, workers' rights to notification of their own test results, and the potential for genetic discrimination in the workplace.

Finally, **Dr. Eula Bingham** (Professor, UC Department of Environmental Health) led a discussion on occupational genetic testing. She explained that benzidine is a potent chemical that causes cancer of the urinary bladder. She asked members of the audience to consider themselves workers in a factory where there is a significant risk of exposure to benzidine. She handed out envelopes to members in the audience. Each envelope contained the "imaginary results of a genetic test" for susceptibility to benzidine toxicity. To those who had a "positive" test, she asked what this might mean to them as workers. Then, to those who had a "negative" test, she asked them to consider whether they should stop being concerned about further continuous benzidine exposure in the future. This demonstration illustrated the dilemma in which workers might find themselves—whether their genetic susceptibility test results turn out "positive" or "negative!"

All in all, the Town Meeting and Symposium were very successful in ***[a]*** promoting the interactions of local neighborhood groups with local and federal government officials and university faculty, ***[b]*** emphasizing the difficulties of gauging risks from environmental exposures, which are often to complex mixtures, and ***[c]*** appreciating the importance of individual genetic variation in the degree of risk of toxicity and cancer.

---***Contributed by Susan Vandale.***

Poster graphics used at the Town Meeting

More on Fen-Phen Therapy

Treatment with the appetite-suppressant drugs fenfluramine and dexfenfluramine, alone or in combination with phentermine, has been associated with cardiac-valve abnormalities [***Interface***, issue #12]. Between 30% and 38% of patients who had taken fen-phen therapy were reported to have these heart-valve anomalies. Fourteen million prescriptions had been written before these drugs were withdrawn by the Food and Drug Administration in September 1997. Follow-up studies now show that "mild-to-moderate valvular involvement associated with this therapeutic regimen" is at least partially reversible.

Interestingly, obesity--which can cause increases in biogenic amines--is associated with increased hypertrophy of certain cell types, and the reversibility of valvular damage is less likely to happen in the more obese patient [*N Engl J Med* **339:** 765 & 771, 1998]. These findings are consistent with what was hypothesized (stimulation of cell division by certain biogenic amines) in our issue #12 article on this subject.

Migration of Animals and Plants: DNA Proof!

One of the spin-offs of the genomics revolution and the Human Genome Project is that we can now take DNA from a drop of blood and determine (without a doubt, or perhaps a "likelihood of one in eight billion") the exact human from which this DNA came! The same would obviously be true for any outbred or randombred cow, mouse, etc. in the world.

Along these lines, an "endemic Hawaiian sunflower" (*Hesperomannia*) has been shown to have originated from the African *Vernonia* species between 26 and 17 million years ago and migrated to Hawaii via southeast Pacific island chains that served as stepping stones [***Proc Natl Acad Sci USA* 95:** 15440, 1998]. Mitochondrial DNA from the Pacific rat (*Rattus exulans*), because it often hitches a ride in Polynesian boats, has been used to trace the migration of ancestral Polynesians**;** the DNA from this rat was a better indicator in this case than the humans—who show a lot of genetic admixture both prehistoric and post-European [***Proc Natl Acad Sci USA* 95:** 15145, 1998]. Investigators have even followed the life of an individual whale, from its conception in the North Atlantic to a raw meat market in Osaka, Japan, 4 years later [***Nature* 397:** 307, 1999]! Native Americans—from Southern Argentina to the northernmost stretches of North America—have a particular Y chromosome that can be traced to two small Siberian ethnic groups [***Science* 283:** 1439, 1999].

Harmful Mutations—Rare or Frequent?

Estimating a "total mutation rate" is done by checking the number of neutral mutations (those that neither impair nor enhance the organism carrying them) through each generation of that organism. By comparing the noncoding regions [***J Theor Biol* 175:** 583, 1995] and amino-acid coding regions [***Nature* 397:** 344, 1999] of humans, chimpanzees and gorillas—recent studies have shown that the number of mutations that arise is surprisingly high. A total rate of **4.2** mutations per person per generation, and a deleterious mutation rate of **1.6** per person per generation, was found in humans**;** the rates were similar in chimpanzees and gorillas. Such studies indicate that many, if not all, human genes are going to be found to be far more ***polymorphic*** (*i.e.* any particular gene in an individual is likely to differ—at one or more nucleotide positions—from that in another individual). This degree of interindividual variation is surprising to many, and was certainly not anticipated several years ago!

Thomas Jefferson, Revisited

As mentioned in our last issue, the 5 Nov 98 article in the journal ***Nature*** by Eugene Foster (Charlottesville VA), six British geneticists and a Dutch statistician, was titled "Jefferson fathered slave's last child." Eric Lander (MIT) and Joseph Ellis (history teacher, Mount Holyoke College) wrote an accompanying article entitled "Founding father" with a subheading "Now, DNA analysis confirms that Jefferson was indeed the father of at least one of Hemings' children." These titles were surprisingly subjective and misleading. Reed Irvine, director of ***Accuracy in Media*** (Washington DC) noted that the Lander and Ellis article suggested that here was a "scientific" report proving that Jefferson "also had a problem with young women, thereby minimizing the Clinton-Lewinsky affair."

Jefferson's wife died in 1782, when her half-sister Sally Hemings was 10 years old. Eston Hemings was born in 1808, when his mother Sally was 36 years old, and Jefferson was 65 years old and had been a widower for 26 years. Herbert Barger (Fort Washington, Maryland), who is a genealogist and husband of a Jefferson family descendant and who helped locate the family members and obtain blood samples, argues that the most likely father of Eston is--Jefferson's brother Randolph 53 years old at the time, who lived 20 miles away. Randolph's son Isham was Sally's age and is another prospect. Others believe that Thomas Jefferson's sister's sons Samuel and Peter Carr, who lived at Monticello with Sally Hemings, are the most likely possibilities. All that can be said, ***scientifically***, is that "a present-day descendant of Eston Hemings was found to have a 'Jefferson-like' DNA pattern on the Y chromosome. Therefore, chances are at least 100 times more likely that any one of about 11 males in the Jefferson family tree was the father of Sally's last son--than if someone unrelated to Jefferson was the father."

Example of What a Microarray Can Do

Patrick Brown's laboratory at Stanford University placed 8,600 human genes on a DNA chip (this concept was discussed in issue #12) and found that the ***addition of serum*** not only stimulates the group of genes needed in ***cell division***, but that genes required for ***wound healing*** are also up-regulated [***Science*** **283:** 83, 1999]. The experiments were aided by a computer program that detects and semi-quantitates the 500 most active genes.

This elegant experiment further underscores the power of DNA chips and microarray assays for looking at how entire batteries of genes coordinate their activity—in response to a particular endogenous (or environmental) stimulus. As Harold Varmus (NIH director) said in December at the Annual Meeting of the American Society for Cell Biology, eventually we will be "looking at the totality of gene behavior in individual cells," even in whole organisms, with such microarrays. This approach "is going to change our view of how life works."

CEG Members in the News

Bruce Aronow chaired an NIH Study Section on bioinformatics and biotechnology, March 1999. He also gave an invited talk at a Gordon Conference on "Clusterin (ApoJ) and ApoE in normal and pathological tissue remodeling," (January 1999, Ventura, California).

Michael Carty was an invited member of a National Institute of Environmental Health Sciences Special Emphases Review Panel, to review proposals in the NIEHS Small Business Innovative Research (SBIR) program (April 1999, Research Triangle Park, North Carolina)

Tom Doetschman was invited to give seminars on the cardiovascular functions of the FGF2 knockout mouse at the following places: University of Louisville School of Dentistry, Department of Biological and Biophysical Sciences, March 1999 (Kentucky); at Wright State University, School of Medicine, April 1999, (Ohio); and at USC School of Medicine, Department of Biochemistry and Molecular Biology (April 1999, Los Angeles, California).

Dan Nebert was invited to speak about the latest in the development of transgenic mouse lines that can receive different human alleles by means of "gene-swapping" methodologies. His talk was given at the "Toxicology Biomarkers Breakout Session" during the National Institutes of Health/U.S. Food and Drug Administration (NIH/FDA) Conference on "Biomarkers and Surrogate Endpoints: Clinical Research and Applications" (April 1999, Bethesda, Maryland).

Alvaro Puga was awarded the 1999 Zeneca Lectureship Prize from the Society of Toxicology in recognition for excellence in research and service to toxicology. He gave a lecture on ***"Environmental factors in heart disease"*** and chaired a session in the 2nd International Colloquium on Transcription Factors as Therapeutic Targets (March 1999, Nancy, France).

Nancy Steinberg-Warren participated in a folic acid focus group organized by the Genetic Program Office of the Department of Health. She was interviewed by Channel 5 News on the subject of folic acid and the prevention of birth defects. Under her direction the Graduate Program in Genetic Counseling of the University of Cincinnati and Children's Hospital Medical Center was granted full accreditation by the American Board of Genetic Counseling for a period of 6 years after completion of an extensive self-study and site visit process.

David Warshawsky delivered an invited seminar at the University of Florida (Gainesville) on ***"Biological consequences of DNA adducts and Ras activation"*** (December 1998).

CEG - SPONSORED SPEAKERS

J. Steven Leeder, PharmD
Director, NICHD Pediatrics Pharmacology Research Unit,
The Childrens Mercy Hospital,
Kansas City, Missouri
11 February 1999 ***"Drug bioactivation and immune responses in the pathogenesis of idiosyncratic drug hypersensitivity reactions"***

William E. Evans, PharmD
Chair, Pharmaceutical Sciences
St. Jude Childrens Research Hospital
Memphis, Tennessee
25 March 1999 ***"Genetic polymorphisms of thiopurine S-methyltransferase: Molecular mechanisms and clinical importance"***

SCIENCE LITE

Imagine -- instead of cryptic, jargon-rich text strings -- your computer gave you error messages in Haiku:

(Haiku is a form of Japanese poetry starting with five syllables, followed by a line of seven syllables, then a concluding line with five syllables)

Chaos reigns within.
Reflect, repent and reboot.
Order shall return.

Aborted effort:
Close all that you have opened.
You ask far too much.

With searching comes loss
And the presence of absence;
"My Novel" not found.

Is the file that big?
It might be very useful.
But now it is gone.

The Tao that is seen
Is not the true Tao until
You bring fresh toner.

Windows NT crashed.
I am the Blue Screen of Death.
No one hears your screams.

A crash reduces
Your expensive computer
To mere grains of sand.

Yesterday it worked.
Today it is not working.
Windows is like that.

Three things are certain:
Death, taxes and lost data
Guess which has occurred.

You step in the stream,
But the water has moved on.
This page is not here.

Out of memory.
We wish to hold the whole sky,
But we never will.

Having been erased,
The document you're seeking
Must now be retyped.

Rather than a beep,
Or a rude error message,
These words: file not found.

Serious error.
All shortcuts have disappeared.
Screen. Mind. Both are blank.

First snow, then silence.
This thousand dollar screen dies
So beautifully.

Stay the patient course.
Of little worth is your ire;
The network is down.

The Web site you seek
Cannot be located but
Endless others can.

Here is proof that music is in our genes!

Further Refinement of CGAP

The methodology of the Cancer Genome Anatomy Project (***CGAP***) was described in issue #11**:** messenger RNAs from a tumor section on a glass slide can be "captured" by laser-activated adhesion to plastic film, reverse-transcribed to cDNA, and then sequenced to see which genes are being up- or down-regulated during various stages of malignancy. A histological field of about 5,000 cells was required, and we suggested that the ability to go to a much lower number of cells would have tremendous impact on many research fields—in addition to the study of cancer. This technique would be wonderful for developmental biologists, in particular. For example, what genes are being up- or down-regulated in the specific cells that fuse the palatal shelves during embryogenesis? Can we look at such specific cells, without any contamination of nearby unwanted cells? Now a laser microbeam microdissection (LMM) method has been shown [*Nature Biotechnol* **16:** 737, 1998] to be successful in single cells! By a phenomenon of laser pressure catapulting (LPC) of cells located in formalin-fixed or paraffin-embedded tissue sections, Schütze and Lahr demonstrated they can "catapult" the chosen cell or small cluster of cells away from the surrounding tissue and onto the cap of a microfuge tube!

An Entire Genome, Sequenced Twice!

Helicobacter pylori is a major cause of gastric inflammation, peptic ulcer, stomach cancer, and mucosal-associated lymphoma. The complete genomic sequences of two unrelated isolates of this bacterium have now been completed so that comparisons can be made [***Nature* 397:** 176, 1999]. The overall genomic organization, gene order, and sets of proteins encoded by the genomes from the two strains are quite similar. However, between 6% and 7% of the genes are specific to each strain, and almost half of these genes are clustered in a single hypervariable region. As a few more genomes from the same genus and species become completely sequenced, we will begin to understand whether this observation is unique to *Helicobacter pylori* or is a more common phenomenon. For example, how different would the entire genome of a sub-Saharan African be from that of a North American Inuit Eskimo?

Observations by a Biologist

Why don't female Grizzly Bears develop osteoporosis?

In Alaska the mating season for Grizzly Bears is such that the female is quite pregnant when she begins hibernation for the long, cold winter. Usually in late November or early December one to three hairless tiny newborn bears (actually, they are still officially called "fetuses") emerge from the uterus and climb the abdominal wall of their sleeping mom to find the milk supply. Lactation continues for the next 4-5 months of winter, while the cubs are growing and the mother continues to sleep without eating anything. Amazingly, ***no osteoporosis*** (thinning of the bones due to decreased body calcium supplies, detectable by x-ray) has ever been found in these Grizzly Bear mothers! Cholecalciferol (vitamin D3) requires two metabolic steps to form 1α,25-dihydroxy-D3, which is by far the most potent ligand for the vitamin D receptor (VDR). The ligand-activated VDR participates in the increased mobilization of calcium from bone (which can cause osteoporosis) and increased absorption of calcium from the intestine (which might help prevent osteoporosis). Understanding what happens, or what doesn't happen, in these hibernating Grizzlies might help us to understand and possibly treat or prevent osteoporosis from occurring in postmenopausal women.

John J. Duffy, 1939-1999

Everyone in the Center for Environmental Genetics (CEG) was greatly saddened to hear about the recent loss of John Duffy, who died in early February of lung cancer. John had been in charge of the Gene Targeting and Knockout Mouse Facilities & Services Core since 1994 and very helpful in generating dozens of knockout mouse lines for CEG members, as well as for other University of Cincinnati laboratories. He was particularly generous with his time and dedicated to members of the CEG—in planning the design of their targeting constructs and in development of the mouse lines. John was one of those selfless unsung heroes of our research community, and he will be sincerely missed by each of us.

LETTERS TO THE EDITOR

RESPONSES/COMMENTS TO VARIOUS QUESTIONS

COMMENT **In our NewsLetter issue #12, it was proposed that the reason for abnormal heart valve morphology following "fen-phen" therapy might be related to the fact that numerous endogenous (as well as exogenous) biogenic amines are known to cause cell type-specific proliferation. Now comes a whole new class of compounds: cyclosporin (an 11-amino-acid metabolite from a fungus) and a related drug "FK506"—which have long been used to treat autoimmune diseases and prevent rejection in bone marrow and organ transplantation. It had always been presumed that cyclosporin increases one's risk of cancer because of suppression of the immune system. Cyclosporin has now been shown to increase cell division of tumors in culture and in the intact animal by inducing the synthesis of transforming growth factor-β (TGFβ). Although this radically different concept will need corroboration by other laboratories, the data suggest a provocative "more general role" than previously thought for cyclosporin-dependent signaling pathways in human disease [*Nature* 397: 530, 1999].**

COMMENT **The title of my talk in issue #14 was inaccurately cited. The correct title is "Effect of N-acetyltransferase polymorphism is substrate-dependent: implications for workplace genetic screening," and my talk was given as part of a Roundtable entitled "Impact of the Human Genome Project on Biological Monitoring: Safer Workers, or Brave New Workplace?" — given at the American Industrial Hygiene Conference and Exposition (Atlanta, May 1998). Your response in issue #15 to the query about the title was not completely correct. Cigarette smokers who are slow acetylators (exposed to 4-aminobiphenyl [4AB] in the smoke) do have higher levels of DNA damage than do smokers who are rapid acetylators. We found that the same was *not* true, however, in benzidine dye workers: acetylation status had no detectable effect, whereas exposure levels and urinary pH explained almost all variation in the data; this means that a small change in exposure (*i.e.* substrate for NAT2) can completely conceal any impact by the NAT2 phenotype.**

The implication is that we cannot make blanket statements or assumptions about "slow acetylators being more susceptible to aromatic amine-induced bladder cancer" without specifying *which* aromatic amine. Each should be tested. An intriguing issue regarding occupational exposure and genetic screening is that, if slow acetylators are "screened out" of the workplace where the exposure is to, say, 4AB, but then the processes change (as industrial processes are wont to do) and benzidine is substituted, then the workers—presumably now all rapid acetylators—would no longer be at decreased risk. What's even worse, the rapid acetylators, or their employers, might allow a higher level of exposure, thinking that they are "resistant" to the effects of these chemicals, when in fact they would be just as sensitive to the risk of urinary bladder cancer from this compound as slow acetylators would be! [*Proc Natl Acad Sci USA* 93: 5084, 1996; *Cancer Epidemiol Biomark Prev* 6: 1039, 1997; *Mutat Res* 393: 199, 1997] — Glenn Talaska

COMMENT **In several of the past issues we have covered the continuing saga of cloning animals, and the ethical implications surrounding the likelihood that humans will eventually be cloned. A small company in Massachusetts has now reported that they had produced a clump of growing embryonic cells by means of transferring a human nucleus into an enucleated oocyte from a cow. In Wisconsin cell lines derived from human blastocysts, when injected into immune-deficient mice, became teratomas (rapidly dividing embryonic stem cells capable of differentiating into many specialized cell types). In Baltimore human embryonic germ (EG) cells derived from fetal gonads**

were shown to form embryoid bodies (able to form multiple differentiated cell types). In Milan neural stem cells, when transplanted into mice whose bone marrow had been destroyed, became blood cells—opening up the possibility that human aplastic anemia and other immunodeficiency disorders might be treatable by human neural stem cells. Harold Varmus, Director of the National Institutes of Health (NIH), issued a legal opinion that research on human embryonic stem cells does not fall under the ban on federal funding for human embryo research [*Nature Biotech* 17: 23, 1999; *Science* 283: 471, 1999; *Nature* 397: 185, 1999].

COMMENT **The movement afoot, to allow online publishing of preprints, is gaining momentum. Because "there is no journal that any scientist reads from cover to cover," a number of colleagues have been pushing for web sites on various subjects (*e.g.* functional genomics, ecogenetics, drug metabolism, etc.) that would allow a particular investigator very rapid and easy access to papers of particular interest. How to have a rigorous peer review online—has not yet been agreed upon, although many argue that one's reputation would rise or fall, depending upon the quality and rigor of any data presented to his peers on the Web [*Science* 283: 1611, 1999].**

COMMENT **The New York city police commissioner proposed the routine, systematic collection of DNA samples from anyone suspected of committing a "fingerprintable" crime, and this proposal was quickly seconded by the New York City mayor. This subject has once again inflamed the DNA testing issue, as we have discussed previously—in numerous issues of this NewsLetter.**

Q **The advantages and dangers of antioxidants such as vitamin C and vitamin E were discussed in issue #5. What is this "vitamin O" that is being advertised in *USA Today* and other newspapers?**

A *The Federal Trade Commission (FTC) is asking a federal judge to bar two Washington State companies from making what the FTC alleges as "false and unsubstantiated claims" about vitamin O. Upon chemical analysis, a Food and Drug Administration (FDA) lab concluded that this "cure for cancer" and other maladies is nothing more than bottled salt water sold for about $10 an ounce.*

COMMENT **In the leading article on "Arsenic-induced toxicity and cancer" (issue #13), emphasis was placed on the likelihood of a human arsenic methyltransferase (AsMT) that had not yet been cloned. Vas Aposhian (Tucson) indicated that he has some evidence for a glutathione-dependent nonenzymatic formation of monomethylarsenic acid "MMA3" and "MMA5" [in which As(III) and As(V) exist] and that methylation might not be a detoxification pathway. Because he detected no AsMT activity in human liver or kidney, it is possible that bacteria in the colon or cecum might be responsible for AsMT in humans.**

Q **Is it true that Craig Venter is planning to sequence more than the human genome in the next 3-4 years?**

A *The National Human Genome Research Institute (NHGRI)—which is funding Gerald Rubin (University of California, Berkeley) and laboratories at the Baylor College of Medicine (Houston) and the Carnegie Institute of Washington (Baltimore)—is joining forces with Venter and his staff at Celera Genomics (Rockville MD) in order to sequence the fruit fly (Drosophila) genome. They predict to have the entire genome sequenced by the end of this year.*

Q **The news has been quiet lately on the proposal (sent to the Iceland Legislature) to study and patent DNA from the entire population of Iceland in order for a company to study complex diseases. What is the current status?**

A *After many discussions and delays, the bill was revised and then passed by almost a two-thirds majority by the Icelandic Legislature, and it has recently become law in Iceland. This privately-owned central database of health records now exists, and anyone interested is encouraged to check it out.* ***http://www.stjr.is/htr***

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Concepts That Cross Species

It has long been thought that tumor suppressor genes only exist in vertebrates, and that disruption of tumor suppressor genes leads to tumors. Although about 50 tumor suppressor genes (homologous to vertebrate tumor suppresssor genes) have been discovered in *Drosophila*, can fruit flies really get cancer? Well, the answer is now yes! Flies were mutagenized and clones of mutant cells in genetic mosaics were examined. Deletion of the *large tumor suppressor* (*lats*) gene led to over-proliferation and tumors in multiple tissues. LATS is a putative protein kinase. The human orthologue, *LATS1*, was cloned and its product was shown to bind to the crucial cell-cycle regulator CDC2 in a cell-cycle-dependent manner. Mice deficient in *Lats1* were shown to be more prone to tumor formation. Finally, re-expression of human *LATS1*—in flies having the mutant *lats* gene—completely suppressed tumor formation [***Nature Genet*** **21:**177, 182, 1999].

In 1995 geneticists working on the small roundworm *Caenorhabditis elegans* stumbled upon a phenomenon now known as "RNA interference," or **RNAi**. Injection of a target RNA is able to cause a loss-of-function, *i.e.* the gene being targeted can be conveniently disrupted! This unexpected phenomenon was believed to be specific to *C.elegans*. Now, however, we know that RNAi is not exclusive to worms. Injecting double-stranded RNA (dsRNA) into *Drosophila* embryos at the syncytial blastoderm stage, Kennerdell and Carthew [***Cell*** **95:** 1017, 1998] have established a loss-of-function protocol in the fruit fly. Since completion of the sequencing of the entire *C.elegans* genome last December (discussed in issue #15), and the predicted completion of sequencing of the entire *D.melanogaster* genome by the end of this year (discussed elsewhere in this issue), RNAi will prove to be an invaluable tool for quickly determining the function of many newly discovered unknown genes in these two animal species. Will RNAi be discovered to occur in vertebrates? In humans? Stay tuned!