Issue Number 7

INTERFACE:

GENES AND THE ENVIRONMENT

CENTER FOR ENVIRONMENTAL GENETICS UNIVERSITY OF CINCINNATI WINTER 1995

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The Community Outreach and Education Program (COEP)

The Community Outreach and Education Program (COEP) is a new Core within the Center for Environmental Genetics (CEG). The COEP Core, headed by **M. Kathryn (Katie) Brown**, supports efforts to identify, design, and coordinate outreach and educational activities in conjunction with community groups, health care providers, educational institutions, and with outreach programs in other NIEHS Centers around the country.

The **Center for Environmental Genetics** is a Center of Excellence sponsored by the National Institute of Environmental Health Sciences (NIEHS); there are approximately two dozen centers around the country. The ultimate goal of the CEG is to conduct research investigations which generate scientific data that can be used to improve the health of community residents, safety in the work place and prevention of environmentally-caused diseases. Since the CEG is funded with federal dollars, it has a responsibility to communicate its research program to the general public, by reporting findings and interpreting the application of the scientific results to everyday life. The COEP Core is the organizational framework put in place to promote this communication.

Definition of "community"

Geography. The geographic focus of the COEP Core is the ***Ohio River Valley***, including the Tristate Area surrounding Cincinnati. For purposes of this Core, the Ohio River Valley includes: Dearborn County in Indiana; Boone, Kenton and Campbell Counties in Kentucky; and Brown, Butler, Clermont, Hamilton and Warren Counties in Ohio (***Figure 1***). The watershed region representing the Ohio River Valley includes: the Whitewater River in Indiana (not to be confused with that name in Arkansas); the Licking River in Kentucky; the Little Miami River, Great Miami River and Mill Creek in Ohio; and the Ohio River which borders all three states.

History. During the past 200 years, industries located along the banks of these rivers--where transportation was convenient, water was always plentiful, and wastes were readily carried away. In time, the Ohio River Valley began to support agricultural, commercial, and heavy industrial developments. The area was settled originally by Germans. By the turn of the century, large numbers of people (looking for employment) migrated into the Ohio River Valley--especially from the Appalachian Mountains and Southern United States.

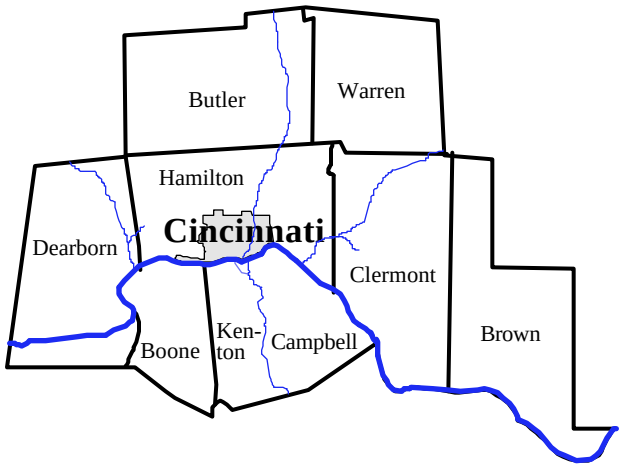

Figure 1. The Ohio River Valley

Environmental problems

Today, political jurisdictions throughout the Ohio River Valley are organizing to address numerous environ-

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mental hazards. Examples of these problems include: the ozone non-attainment status of this urban airshed; the impact of industrial discharges and combined sewer overflows on the local water quality; and the reclamation of properties previously contaminated with organic chemicals, industrial pollutants, and heavy metals.

Urban-Appalachian and African-American communities are struggling to address several of these issues. For example, these communities are addressing issues such as: the clean-up of radioactive wastes and contamination at a former nuclear weapons-processing plant (Fernald); the vertical expansion of a landfill; the odors generated by a municipal sewage-processing facility and a 55-gallon drum-recycling operation; toxic effluent from a paper-recycling operation; and a clean-up of toxic wastes left behind at abandoned industrial sites.

The land-use zoning in these communities mixes high-density residential areas with intermediate- and heavy-manufacturing districts. As heavily industrialized regions such as the Ohio River Valley compete for critical economic growth, a number of issues have become hotly debated. These issues include: environmental justice, environmental and public health, NIMBYism (Not In My Back Yard), comparative risk assessments, and cost-benefit analyses.

What can our COEP Core do?

The current plans of the CEG's COEP Core are to: **[a]** support local community groups' efforts to participate in these discussions and address their concerns; and **[b]** make available--to the institutions and populations residing in the Ohio River Valley--information pertinent to these discussions. By focusing its attention on this geographic region, the entire Center is becoming responsive to the ***environmental health issues and problems of greatest concern*** to the Ohio River Valley, and the CEG will develop ***productive outreach efforts*** that are specifically designed to address locally defined issues.

Institutions. This geographic region is served by the University of Cincinnati Medical Center and the Children's Hospital Medical Center. This region also closely overlaps the membership of the Ohio-Kentucky-Indiana (OKI) Regional Council of Governments--which is the metropolitan (regional) planning organization (MPO). Successful projects that are developed under the auspices of the COEP Core will be made available as model projects to interested communities throughout Ohio, Kentucky and Indiana.

Populations. Pertaining to the ***CEG theme of studying the interactions between genes and the environment***, the Ohio River Valley provides the opportunity for two unique population-based genetic studies. Firstly, the issue of marriages within families among the Appalachian population is a prevailing stereotype that has not been adequately studied. The large Appalachian population in the study area, comprising approximately 40% of the population of Hamilton County, for example, could provide an important entrée to this research topic. Secondly, there are several different Amish communities bordering the study area. In time, these communities might be approached about studying topics of mutual interest.

Organization and goals of our COEP Core

The purpose of CEG's COEP Core is to reach out to local communities, institutions and individuals. We want to collaborate with neighborhood groups in order to help with their environmental and/or public health program initiatives. We also want to develop and implement educational programs which promote the transfer--to the community-at-large--of useful scientific information pertaining to environmental health and environmental genetics. To achieve these objectives, the COEP Core is organized around the following three components:

Community-based outreach and education;
Institution-based outreach and education; and
Mass media outreach and education.

Community-based outreach and education

This component of the COEP Core focuses on working with neighborhood-based organizations to develop and implement environmental health activities that support objectives identified by community group(s). The primary purpose of this modality is to make available to neighborhoods the intellectual and technical resources of both the CEG and the University of Cincinnati. This includes not only the transfer of expertise and the sharing of technical resources (***e.g.*** analytical services), but also the access to other University of Cincinnati resources, including the joint funding of COEP projects. For example, the University of Cincinnati's Institute for Community Partnerships (ICP) supports collaborative outreach efforts that address the community and educational needs of the greater Cincinnati area; monies are made available by the Ohio Board of Regents.

The CEG in the past has supported programs consistent with this objective. For example, several CEG members (**Eula Bingham, Bob Bornschein, Katie Brown**) are co-Investigators on a U.S. Environmental Protection Agency (EPA)-funded Environmental Justice Through Pollution Prevention (EPA EJP2) grant, entitled ***Pollution Prevention: Promoting Environmental Justice in Lower Price Hill.*** This project represents a partnership amongst the University of Cincinnati, the Cincinnati Health Department, the Urban Appalachian Council, and the Lower Price Hill Community Council. The partnership has developed a

community-wide structure for gathering and evaluating information about community values and perceptions. The partnership is also gathering technical data on environmental and public health.

As another example, **Bingham** and **Brown** have worked with the Rural Coalition and several other organizations on the submission of an EPA grant application entitled ***UC-Rural Coalition Collaborative Partnership for Environmental Justice.*** The primary objective of this project is to develop and promote indigenous leadership within the community of Columbia, MS. These community leaders will learn skills, gain information and access resources necessary for successful community-based approaches to characterizing environmental pollution, assessing the effectiveness of environmental monitoring and remediation strategies, evaluating the health status of community residents, and participating in decision making with government and industry to set intervention and remediation strategies.

What is this component of the COEP Core planning in the future? We are seeking ways to develop partnerships, with community-based organizations within our geographic purview, who want to address environmental and/or public health issues. These partnerships might include, for example, collaborating with: **[a]** a local community college to develop and support nontraditional, innovative college courses in genetics and/or environmental science; or **[b]** a youth group to develop hands-on projects in environmental health or genetics--designed to provide participants with opportunities to collect and analyze scientific data pertinent to issues of local concern. These projects will be designed and implemented in conjunction with community-based organizations and individuals, relying on the established strategies of ***collaborative education*** and ***participatory research***.

Collaborative education is based on the premise that learning is most effective when the knowledge, background and skills of the teachers and learners alike are used to develop a curriculum plus the associated learning experiences. ***Participatory research*** is an extension of the principles of collaborative education: students gain access to the technical resources necessary to generate their own research data, and then they coordinate their own project activities and develop their own strategies to address their research findings.

Institution-based outreach and education

This component of the COEP Core focuses on transferring up-to-date information about environmental health sciences and genetics to organizations and institutions in the community. The primary purpose of this modality is to update educators and health-care practitioners about genetic principles, as well as to apply these principles to human health and disease prevention. These projects are designed and implemented in conjunction with a co-sponsoring agency. The ***modular format*** of these seminars and workshops will facilitate the transfer of these programs to other audiences in the future.

The CEG has supported programs consistent with this objective. For example, CEG members (**Wilson Tabor, Bob Bornschein, Kitty Dixon, Joanna Groden, George Leikauf, Grace Lemasters, Jack Loper, Anil Menon**) have worked with Miami University (Oxford, Ohio) on an NIEHS application, entitled ***Teaching Environmental Health: Science/Risks/Choices.*** Geared toward science teachers of children in grades 7 through 12, this application proposes to provide training in various aspects of basic genetics, ecogenetics, human health and disease prevention, biotransformation, epidemiology, and toxicology. These CEG members also plan to help with the selection and development of teaching materials.

What is this component of the COEP Core planning in the future? We hope to develop teaching modules--on the subjects of environmental health sciences or environmental genetics--for inclusion in the science curriculum of elementary and secondary schools. We look forward to designing and implementing, in the Department of Environmental Health at the University of Cincinnati Medical Center, an "interdisciplinary environmental health and genetics" class. This course could be included in the Continuing Education Program curriculum, or a similar continuing education program that would reach occupational and public health professionals. We hope to implement in-service training programs, which will include the subjects of "environmental genetics" and "genetic counseling" for local health-care providers.

This Component of the COEP Core has been working with the ***Medical Genetics Counseling Program*** (located in the Division of Human Genetics, Children's Hospital Medical Center). Their joint plans include the development of educational programs that focus on strengthening the understanding of health-care providers about "the link between human genetics and environmental exposures." At the same time, several CEG members (**Kitty Dixon, Joanna Groden, Grace Lemasters, Anil Menon, Dan Nebert**) serve as faculty to the Master of Science Medical Genetics Counseling Program. They assist with the development and implementation of curriculum; advise and teach students; and support student-initiated environmental genetics research. **Nancy Warren**, co-Director of this M.S. Program, is coordinating these initiatives with the COEP Core.

Mass media outreach and education

This Component of the COEP Core focuses on making information available by way of on-line communications and mass mailings. This information is made available to CEG members, the University of Cincinnati in general, the local community (both urban and rural, as defined above), and to colleagues and lay persons throughout this nation and world-wide. The primary purpose of this modality is to broaden the reach of the CEG by routing information beyond personal and organizational contacts and onto electronic networks.

The CEG has been publishing this NewsLetter, ***Interface***, since the winter of 1993-94. We have also continued to expand and update the CEG homepage on the **World Wide Web** (WWW) since 1995. The current address for the WWW homepage is ***http://www.uc.edu/~matlibrs/ceg.html***. Articles pertaining to COEP projects, as well as community issues and perspectives, are now being included routinely in ***Interface*** and on the WWW homepage. The COEP is seeking to contribute to other electronic bulletin-board networks that are geared toward environmental and public health issues. Examples include Ohio Valley Community Health Information Network (OVCHIN), *Ohio*LINK, Productivity Online, and Telehealth.

New projects

The continuing role of the CEG's COEP is to identify and design new community education and outreach projects. These projects must be responsive to expressed community needs, concerns, and/or interests. Moreover, these projects should be consistent with the objectives of the COEP Core, the mission of the CEG and its theme of "***genes and the environment***," and the NIEHS Office of Communication.

In order to accomplish its ambitious mission, the COEP Core works closely with many different individuals and organizations ***(Figure 2)***. The COEP Core seeks to work with advocacy- and community-based organizations as well as schools and continuing education programs throughout the Ohio River Valley. The COEP Core relies upon members of the CEG, faculty and staff from the University of Cincinnati and the Children's Hospital Medical Center, including the Genetics Counseling Program, to collaborate with these organizations and programs in the development and implementation of community outreach and education projects. The COEP Core also envisions working closely with other CEG Core facilities in the design and conduct of population-based studies. Already, **Grace Lemasters**, head of the Epidemiology/Experimental and Statistical Modeling Facilities and Services (F&S) Core, and **Glenn Talaska**, head of the Internal Dosimetry and Biomarkers F&S Core, are discussing potential projects with the COEP.

COEP funds are being used to defray costs associated with the design and development of relevant projects. CEG members, in conjunction with the COEP, are keen to work with various groups designing and implementing new community outreach and education programs. Individuals interested in organizing and/or participating in COEP projects should contact **M. Kathryn Brown, PhD**, COEP Coordinator--Telephone 513-558-0092; Fax 513-558-4838; e-mail at KATIE.BROWN@UC.EDU

The next issue of ***Interface*** will feature The Rural Coalition, which is part of the Community-Based Outreach and Education Component of the COEP Core.

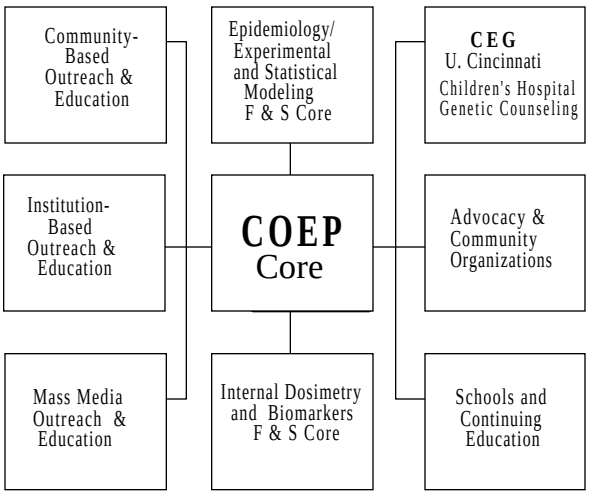

Figure 2. Interactions with the COEP Core

LETTERS TO THE EDITOR

RESPONSES TO VARIOUS QUESTIONS

Q **Cloning of the *BRCA2* gene has hit the newspapers recently. Since it is the next number after the breast cancer gene "*BRCA1*," doesn't this mean that the two genes are near one another on the same chromosome and/or similar in function?**

A *Both genes together are responsible for the vast majority of early-onset hereditary breast and ovarian cancer. As the result of family studies, **BRCA1** was mapped to chromosomal subregion 17q by means of analysis of a set of high-risk kindreds, and then identified 4 years later by the technique of positional cloning (a method discussed in our Issue #4). At about the same time and also as the result of family studies, **BRCA2** was localized to chromosomal subregion 13q. The complete **BRCA2** gene has now been cloned and mutations in chromosome 13q-linked kindreds have been shown. The gene spans more than 70 kilobases and has 27 exons [Nature Genet* **12,** *333-337 (1996)].*

*If the **BRCA1** gene was considered large (coding for 1,863 amino acids), then **BRCA2** is **enormous** (encoding 3,418 amino acids)! There are some similarities between the **BRCA1** and **BRCA2** genes, but the fact that they reside on different chromosomes indicates that the two genes are probably more than 300 million years diverged during evolution. Similarities include: [1] both genes encode exceptionally large, charged proteins; [2] both have a large number of exons, including a very large exon 11 (3,426 base pairs for **BRCA1** and 4,932 base pairs for **BRCA2**); [3] both have a nontranslated first exon; [4] both genes span approximately 70,000 bases; [5] both are expressed at high levels in testis; and [6] both are postulated to be members of the "granin" family. Granins are acid proteins that bind calcium and aggregate in the presence of calcium, are solely neuroendocrine or endocrine in origin, and involved in growth-suppressive effects. Granins contain the 10-residue consensus sequence ENLSxxDxEL. It should be emphasized at this point in time that no functional studies have yet been performed on the BRCA2 protein, and the evidence for the BRCA1 protein acting as a granin is largely circumstantial.*

COMMENT: Back in issue #3 we featured the problem of environmental estrogens and provided the latest information on the *BRCA1* gene, which had just been cloned. The function of the BRCA1 protein is slowly being understood. The latest exciting studies involve the retroviral transfer of the wild-type *BRCA1* gene into cultured cells of breast and ovarian cancer lines and into human breast cancer cells put into the nude (immunodeficient) mouse line. Endocrine-derived tumors--but not colon or lung tumors--were shown to be inhibited by *BRCA1* expression. The retroviral transfer of a mutated *BRCA1* gene was not inhibitory [*Nature Genet* 12, 298-302 (1996)].

***BRCA1* expression was previously shown to be increased during breast development and pregnancy, and to decrease after parturition. Inhibition of *BRCA1* expression (which occurs during Loss Of Heterozygosity, (LOH) in the breast, ovary or prostate of individuals born with only one functional *BRCA1* allele instead of two) was previously known to lead to accelerated growth of both normal and malignant breast cells.**

This past knowledge, coupled with the latest research described above, provides a strong case for the role of the BRCA1 protein in controlling growth of certain endocrine-specific cells. If a mutation occurs in an individual's one remaining "good" *BRCA1* allele, the result is the loss of "normal growth controls" and, hence, the beginning of uncontrolled growth, *i.e.* malignancy.

Q The Human Genome Project is helping to uncover some truly amazing genes! What is this "novelty-seeking gene" recently reported in the New York Times? and would this have any relationship to "genes and the environment," the theme of your Center?

***A** The "Novelty-seeking gene" you ask about is the dopamine D4 receptor **(D4DR)** gene [Nature Genet **12**, 78-81 (1996)]. There are many lines of evidence implicating the relationship between dopamine and novelty-seeking behaviors from animal studies, Parkinson's disease patients, and the effects of dopamine agonists (**e.g.** amphetamines, cocaine, alcohol). As with all dopamine receptors, the* D4DR *is a 7-transmembrane protein whose "third cytosolic loop" (exon III) is believed to be involved in second-messenger signal transduction pathways. There is a human polymorphism in which the* D4DR *protein has been found to contain between two and ten 16-amino acid repeats. The "7-repeat allele" was shown to be highly significantly associated with the human personality trait of "novelty-seeking," as determined by medical history and a self-report questionnaire. This correlation was independent of sex, age or ethnicity.*

*The possibility to bring this "personality gene" into the domain of environmental health is intriguing. But, certainly, choices of lifestyle (**e.g.** smoking, drug or alcohol addiction, risk of HIV) and occupation (hazards in the work place) should cause us to consider this gene as one of the many genes that might be involved in the "multiplex phenotypes" (discussed in our Issue #4) associated with environmental toxicity and cancer.*

CEG Members in the News

Dave Warshawsky gave a presentation entitled ***"Metabolic activation of environmental carcinogenic N-heterocyclic aromatics: biological consequences"*** at the University of Southern California (Los Angeles, California) in March 1996. He has also been elected as Vice Chair of the Ohio Coal Advisory Board, where he will serve as U.S. and State Representative on Environmental Issues.

Dan Nebert was invited to speak in March 1996 at the symposium on "Genes Encoding Drug-Metabolizing Enzymes during Reproduction and Development" at the 16th Annual Meeting of the Society of Toxicology (SOT) in Anaheim, California. The title of his talk was ***"Use of knockout mouse lines to study the role of drug-metabolizing enzymes and receptors during reproduction and development."*** He will also give a Plenary Lecture on the same subject at the 36th Annual Meeting of the Teratology Society in June 1996 (Keystone, Colorado). He has also been invited to be the Keynote Speaker for the "Visions in

Pharmacology" Research Day at the University of Toronto in May 1996, where his talk is entitled ***"Three decades: a pathway of toxicity, cancer, and oxidative stress."***

Frank McCormack gave a talk entitled ***"Structure/Function analyses of surfactant protein A in transgenic mice"*** at the University of Toronto and University of Western Ontario (Ontario, Canada) in February, 1996.

Sohaib Khan visited the Center of Advanced Molecular Biology (Lahore, Pakistan) in December 1995 to review their program in steroid receptor research. He also gave a seminar on ***"Estrogen receptor mutations in breast cancer."***

Dan Hassett gave a seminar in February 1996 at Miami University (Oxford, Ohio), entitled ***"Iron and the ferric uptake regulatory protein in the control of alginate activation by* Pseudomonas aeruginosa."**

Nancy Steinberg Warren was invited to give a presentation on ***"Genetic Counseling"*** at the Quarterly Clinical Services Update Meeting for the Northern Kentucky District Health Department Nurses in January, 1996 (Newport, Kentucky).

Greg Grabowski gave a talk entitled ***"Advances in Gaucher Disease"*** at Northwestern University Colloquium (Chicago, Illinois) in December, 1995. He was also invited to speak at the Annual Meeting of the American Association of Professors of Human and Medical Genetics (Orlando, Florida) in January, 1996. The title was ***"Curriculum development for human genetics."***

Jack Loper is one of four CEG members involved in the UC/NIEHS Superfund Basic Research Program ***"Microbial Detoxification/Degradation of Hazardous Wastes."*** Several of these projects examine the biodegradation of azo dyes, which are a public health concern because the dyes and their byproducts can give rise to carcinogenic intermediates. This work has led to a potential collaboration with researchers at the National Autonomous University of Mexico (UNAM) in Mexico City, where the focus is on biological treatment of textile wastes.

SCIENCE LITE

How Do YOU Hunt Elephants?

- MATHEMATICIANS hunt elephants by going to Africa, throwing out everything that is not an elephant, and catching one of whatever is left.
- EXPERIENCED MATHEMATICIANS will attempt to prove the existence of at least one unique elephant before proceeding to step #1 as a subordinate exercise.
- PROFESSORS OF MATHEMATICS will prove the existence of at least one unique elephant and then leave the detection and capture of an actual elephant as an exercise for their graduate students.
- COMPUTER SCIENTISTS hunt elephants by exercising Algorithm A:
  1. Go to Africa.
  2. Start at the Cape of Good Hope.
  3. Work northward in an orderly manner, traversing the continent alternately east and west. During each traverse pass:
     a. Catch each animal seen.
     b. Compare each animal caught to a known elephant.
     c. Stop when a match is detected.
- EXPERIENCED COMPUTER PROGRAMMERS modify Algorithm A by placing a known elephant in Cairo to ensure that the algorithm will terminate.
- ASSEMBLY LANGUAGE PROGRAMMERS prefer to execute Algorithm A on their hands and knees.
- DATABASE ADMINISTRATORS do not need to go out and capture elephants when they can retrieve them simply with an ad hoc query:

```
1 SELECT * FROM AFRICAN_CRITTERS
2 WHERE CRITTER_TYPE ='TERRESTRIAL'
3 AND SIZE = 'LARGE'
4 AND COLOR = 'GRAY'
5 AND TRUNK = 'YES'
6 AND ODOR IS NOT NULL
```

- ENGINEERS hunt elephants by going to Africa, catching gray animals at random, and stopping when any one of them weighs $\pm$15 percent of any previously observed elephant.
- SYSTEMS INTEGRATION ENGINEERS are not so concerned with hunting elephants as with creating a seamless interface between the elephants and their environment.
- ECONOMISTS don't hunt elephants. But they believe that, if elephants are paid enough, they will hunt themselves.
- STATISTICIANS hunt the first animal they see N times and call it an elephant.
- CONSULTANTS don't hunt elephants, and many have never hunted anything at all, but they can be hired by the hour to advise those people who do.
- OPERATIONS RESEARCH CONSULTANTS can measure the correlation of hat size and bullet color to the efficiency of elephant-hunting strategies, if someone else would only identify the elephants.
- POLITICIANS don't hunt elephants, but they will share the elephants you catch with the people who voted for them, and pass legislation to create larger committees to keep this activity going for many decades.
- LAWYERS don't hunt elephants, but they do follow the herds around arguing about who owns the droppings.
- SOFTWARE LAWYERS will claim that they own an entire herd based on the look and feel of one dropping.

- VICE PRESIDENTS OF ENGINEERING, RESEARCH, AND DEVELOPMENT try hard to hunt elephants, but their staffs are designed to prevent it. When the vice president does get to hunt elephants, the staff will try to ensure that all possible elephants are completely prehunted before the vice president sees them. If the vice president does see a non-prehunted elephant (in other words, a live one), the staff will (1) compliment the vice president on his keen eyesight and (2) enlarge itself to prevent any recurrence.
- SENIOR MANAGERS set broad elephant-hunting policies--based on the assumption that elephants are just like fieldmice, but with deeper voices.
- QUALITY ASSURANCE INSPECTORS ignore the elephants and look for mistakes the other hunters made when they were packing the jeep.
- SALES PEOPLE don't hunt elephants but spend their time selling elephants they haven't caught, for delivery two days before the season opens.
- SOFTWARE SALES PEOPLE ship the first thing they catch and write up an invoice for an elephant.
- HARDWARE SALES PEOPLE catch rabbits, paint them gray, and sell them as desktop elephants.
- NIEHS CENTER DIRECTORS will look for any possible association between hunting elephants and environmental toxicology and/or public health issues--so that an RFA (request for grant applications) might be drawn up to help support federally funded research.

"I know you believe you understand what you think I said, but I am not sure you realize that what you heard is not what I meant." ***---The statistician***

------Extracted from the Internet and, of course, modified a bit

DNA and Doggie Do-Do

Talk about the relevance to the Human Genome Project and "genes and the environment"! The 150 residents of the British village Bruntingthorpe have decided to establish a means to identify the "owner of inappropriately placed dog manure" by DNA analysis. Just a few hairs from each of the 30 or so hounds in the village will be used to create a genetic profile, which can then be used to match against offending sidewalk specimens that have not been taken care of by their owner in a responsible manner.

Dr. Ian Eperon, the village geneticist who suggested this project, indicates that the local dog-owners will likely cooperate--in order to not have any "clouds of suspicion" surrounding them. Graduate students will probably be asked to work on this project, because they will need someone (who will work for next to nothing) to collect the evidence. **Anil Menon**, head of the CEG's Genetic Analysis and Phenotyping Facilities and Services Core, expects to become a consultant for this project.

1995 Nobel Laureates study development in fruit flies

Some of us have heard the criticism at site visits or study sections: "If you propose to study ***human*** environmental toxicology, why would one ever choose to study the mouse? The fruit fly? Or the nematode? You should do your work on the human!" The 1995 Nobel Prize for Physiology or Medicine is a wonderful statement for the importance of basic research, as contrasted with "applied science." Three developmental biologists--Edward B. Lewis (professor emeritus; California Institute of Technology), Christiane Nüsslein-Volhard (Max Planck Institute, Tübingen), and Eric F. Wieschaus (Princeton University)--have shown that a ***genetic approach*** can be successfully used to study how genes control a seemingly very complicated "***multiplex phenotype***": early embryonic development in *Drosophila melanogaster*.

Early in his career, Lewis chose to study fruit fly mutations in which entire body parts appear in unexpected locations (*e.g.* an extra pair of wings, a pair of feet in place of antennae). For example, he realized that, for flies with an extra pair of wings, an entire segment of the thorax had been omitted and replaced by a duplicate of the segment just in front of it. Over decades of collecting mutants, cross-breeding them and mapping the abnormalities, Lewis identified a series of control genes (later named "***homeobox*** selector genes"). Although Lewis' work did not explain critical ("upstream") events that lead to "selector gene" activation in the first place, this exciting field of research was exploited in the late 1970s by Nüsslein-Volhard and Wieschaus, who were in Heidelberg, Germany at the time. Following their 1980 watershed paper in ***Nature***, it became commonly accepted that: "[1] differing concentrations of a maternal gene product first activate the ***GAP*** genes, dividing the embryo into broad regions; [2] the ***pair-rule*** genes then subdivide these regions into segments; and [3] finally, the ***segment-polarity*** genes set up repeating anterior-to-posterior structures in each segment." The ***homeotic*** genes, first appreciated by Lewis, are activated by the ***GAP*** genes and further controlled by the ***pair-rule*** genes and the ***segment-polarity*** genes.

Diseases involving birth defects that can now be explained by this basic science research include: mutations in a human gene related to the fruit fly ***pair-rule*** gene, ***paired***, that causes Waardenburg's Syndrome (broad-set eyes, partial albinism and hearing loss); and a chicken ***segment-polarity*** gene, ***Sonic hedgehog***, that plays an important role in determining left-right symmetry. Intriguingly, the ***homeobox*** genes are also postulated to have played a major role in ***evolution***--when a burst of creativity formed virtually all phyla during a 10-million-year segment of the Cambrian Period about 540 million years ago [see ***Time*** magazine, pp 66-74, 4 Dec 1995].

Observations by a Biologist

Is there a mouse gene for "Couch Potato"?

At the end of the fifth grade last spring, my daughter brought home two female white mice as pets. Wanting to show the kids some "coat-color genetics," I purchased a black-and-white spotted male. He looked enough like a cow, so his name became "Moo."

Wham! We soon had all the genetic possibilities that one could ask for! As some of you may know, the four major coat-color loci (out of more than 60 genes that affect coat color) are ***a, b, c*** and ***d***, which encode the traits agouti (chinchilla color), black, white and dilute, respectively. And, with Moo introduced into our colony, we were able to make strong hypotheses about the alleles at these loci for the two females and Moo. Agouti wild-type (***+/+***) is dominant over ***a/a*** and epistatic (highest in the pecking order) to everything else. Since we did not have the wild-mouse agouti color, we obviously had mice with ***a/a*** alleles.

The albino locus, ***c*** (encoding for tyrosinase), is epistatic over ***b*** and ***d***--meaning ***c/c*** homozygotes are white, whereas ***+/c*** and ***+/+*** at the ***c*** locus enable other colors to occur. So, now we knew that the genotype of our white females is ***a/a, c/c***. The coat colors of the children and grandchildren (F_1 and F_2 generations) included black-nondilute and brown-nondilute (***+/+, +/+*** and ***b/b, +/+*** at the ***b*** and ***d*** loci, respectively), grey (black, dilute), and tan (brown, dilute) (***+/+, d/d*** and ***b/b, d/d*** at the ***b*** and ***d*** loci, respectively). Re-emergence of Moo's spotted trait in the F_2 generation--at a ratio of about one in four, and independent of sex--confirmed that the "spotted" phenotype is inherited as an autosomal recessive trait. Because the F_1 babies were not spotted, this also confirmed that "spotted" is recessive.

The coat colors of the "spotted" mice included black, grey, brown and tan with white--confirming a separate locus for "spotted." The color combinations and healthy appearance also make these mice look very cute!

We also purchased a 6-inch plastic wheel and noticed that, while most of the mice wanted to run for hours on the wheel, a few absolutely refused. Having an "interest in exercise" appeared to be codominant (additive, gene-dose) over the "couch potato" allele (***Figure 3***). Given a quantitative assay for assessing this phenotype, **Anil Menon** and **John Lorenz** in the CEG's Genetic Analysis and Phenotyping Facilities and Services Core would be able to determine **[a]** if more than one gene were involved, and **[b]** the subchromosomal location of these gene(s)! And then, on to human populations! Are there "exercise-interested" and "couch-potato" humans? Undoubtedly!

This is an example of what can be done in this Center. It is now possible to correlate phenotypes (traits such as enhanced sensitivity to aerosol aldehydes in the work place, or heavy-metal exposure in the community) with one or more particular genes.

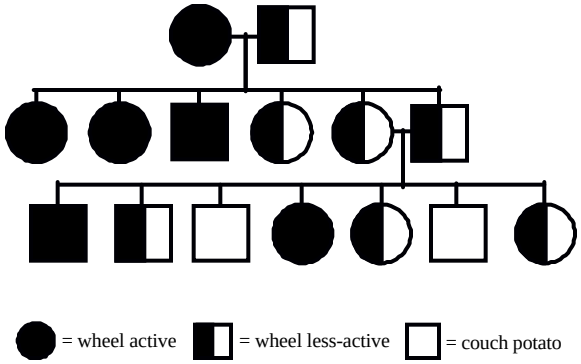

Figure 3. A "Couch Potato" pedigree

INTERFACE is supported by NIH grant # ES06096 from the National Institute of Environmental Health Sciences, and is published by the University of Cincinnati Center for Environmental Genetics, Daniel W. Nebert, M.D., Director

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