Issue Number 14

INTERFACE:
GENES AND THE ENVIRONMENT

CENTER FOR ENVIRONMENTAL GENETICS UNIVERSITY OF CINCINNATI SPRING 1998

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Toxic Effects of Polyhalogenated Biphenyls

Biphenyls are "two benzene rings linked together." ***Polyhalogenated*** means "to contain multiple halogen atoms such as chlorines or bromines." Polychlorinated biphenyls (PCBs) and their closely related cousins, the polybrominated biphenyls (PBBs), are widespread environmental contaminants—found in discarded transformers, machine lubricants and refrigerants. Even though environmental concentrations of these chemicals are generally very low, PCBs and PBBs are industrial byproducts that have been identified extensively in virtually all components of the global ecosystem, including human tissues, and there is a great clinical concern because of the possible toxic and carcinogenic effects of polyhalogenated biphenyls.

There is a large literature about exposure of humans who eat dioxin- and PCB/PBB-contaminated fish. These agents have been implicated and extensively studied, with regard to their role in overt environmental toxicity (*e.g.* immunosuppression) and cancer. It has not been as well appreciated, however, that exposure to PCBs and PBBs, and bioaccumulation of potentially deleterious PCB/ PBB concentrations—via contaminated landfills and drinking water, and consumption of fish—may lead to subtle neurological and central nervous system (CNS) toxicity and alterations in behavior, including changes in IQ. In this article we will concentrate on this latter subject.

Chemistry and Subcellular Effects

PCBs and PBBs have a biphenyl backbone (***Figure 1***) and generally are a mixture of compounds containing between 2 and 10 halogens**;** for example, "Aroclor 1246" and "1254" denote 12 carbon atoms and 46% and 54%, respectively, of the biphenyl hydrogens replaced by chlorine (on average) in the mixture. The chemical and physical properties that have made these compounds so well suited to their industrial applications are also responsible for their persistence in the environment and in their bioaccumulation (in plants, in fish, and in humans at the end of the food chain). The toxicity and carcinogenicity of these compounds likely occur via metabolic formation of reactive intermediates that damage DNA, RNA and protein—a "***genotoxic***" mechanism (which has been extensively studied for more than 25 years)—and via endogenous receptors and signal transduction pathway(s), a "***nongenotoxic***" mechanism (appreciated only during the past decade).

PCBs and PBBs have been found to elicit a potent biochemical response as a function of their affinity for cellular receptors. The number of halogens and their positioning around the biphenyl structure are critical in determining the activity of these halogenated hydrocarbons. For example, halogens in the *meta*- or *para*-positions **[*Figure 1, left*]** allow the molecule to remain planar and, hence, to bind to the dioxin-binding Ah receptor (AHR), and to elicit effects similar to those seen for AHR ligands such as polycyclic hydrocarbons (*e.g.* benzo[a]pyrene) and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD; dioxin). On the other hand, halogens in the *ortho*-positions of one phenyl ring interfere with *ortho* halogens in the other phenyl ring **[*Figure 1, right*]**, thereby making the molecule nonplanar and thus unable to bind to the

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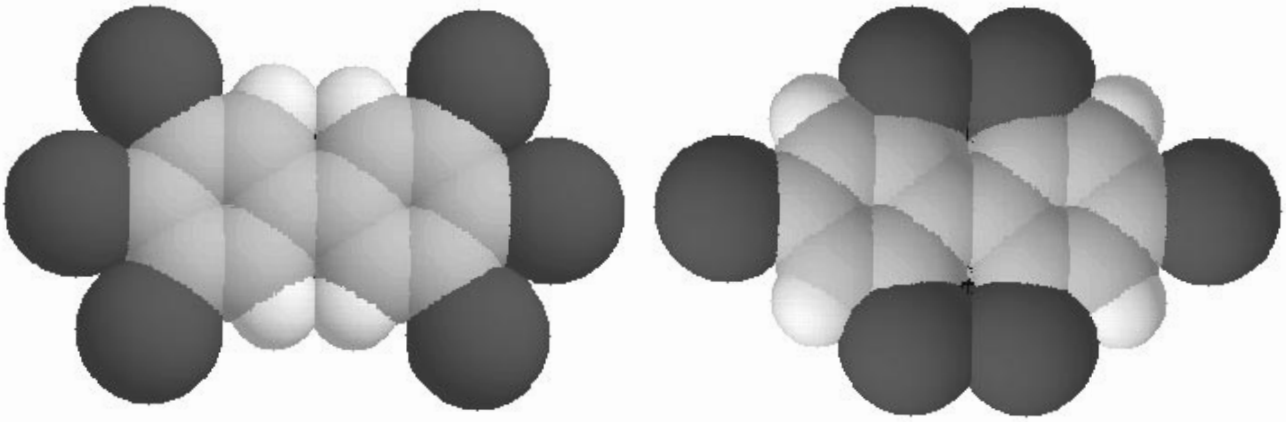

Figure 1. Hexabromobiphenyls are shown as space-filling models. *Left*: 3,4,5,3',4'.5'-hexabromobiphenyl. *Right*: 2,4,6,2',4',6'-hexabromobiphenyl. Note the overlap in the molecular orbits of the ortho bromines, causing the ortho-substituted biphenyls to rotate around the [1-1'] bond.

AHR. Numerous studies over more than two decades, however, have shown that such a nonplanar molecule can elicit an induction response similar to that seen for phenobarbital. Although it is very likely that a phenobarbital receptor does exist, it has not yet been identifed and characterized.

Several PCB and PBB congeners are noteworthy environmental agents because **: (a)** they persist for years in animals and in the soil**; (b)** they are genotoxic (DNA-damaging)**; (c)** the toxicity and carcinogenicity of specific isomers are often inversely proportional to their capacity to form DNA adducts, emphasizing again the importance of a nongenotoxic (*i.e.* receptor-mediated) rather than a genotoxic mechanism of action**; (d)** they have been shown to be potent tumor promoters when, for example, the genotoxic mutagen diethylnitrosamine is given as the tumor initator**; (e)** they are immunotoxic**; (f)** they disrupt sex hormone endocrine and cholesterol pathways and thyroid functions**; (g)** when administered together with iron, they are more carcinogenic and porphyrogenic than when given alone, suggesting a mechanism of oxidative stress-mediated toxicity**;** and **(h)** they cause toxicity to, and subtle effects on, the CNS, but the mechanisms of this developmental toxicity remain completely unknown. PCBs have been much more extensively studied than PBBs, for reasons not clear**;** however, the structure-activity relationships of the chlorinated and brominated biphenyl congeners to toxicity and cancer are identical.

The FireMaster Disaster

In 1973 more than 10,000 Southern Michigan residents (principally farm families and their neighbors) were accidentally exposed to about 1,000 pounds of PBBs. The flame retardant "FireMaster" was mistaken on a shipping dock for the cattle food "NutriMaster," and thousands of cows, pigs and chickens were inadvertently fed the PBB-containing FireMaster and had to be destroyed. Humans ate the meat, milk and eggs from the contaminated farm animals before the magnitude of the danger had become apparent. Twenty-five years later, PBB levels (370 times higher in adipose tissue than in blood) continue to decrease in this exposed population at a rate of 7% per year.

PBB Effects on the CNS

Intriguingly, the earliest clinical signs that a disaster had occurred included amnesia, confusion and somnolence (farmers forgot the location of their tractors, were unable to find their way home at the end of the day, and fell asleep in the fields) and leukocytopenia (lowered white blood cell count, *i.e.* evidence of immunosuppression). Also reported was chloracne (a type of skin rash)—which is also the sentinel sign of dioxin (AHR-mediated) toxicity in exposed workers. Decreased birth weights, increased respiratory illnesses, and lower I.Q. values among children born to Michigan mothers exposed in 1973-74 have been reported, and the mental development of these children continues to be followed into adulthood.

Other recent studies on polyhalogenated biphenyls included (a) one in Michigan in which contaminated fish from the Great Lakes was the source of PCBs in pregnant women, and (b) one in North Carolina in which the source of PCBs in perinatal exposure to PCBs was via breast milk. Studies on these two PCB-exposed populations have carefully estimated intrauterine exposure, and neurobehavioral assessments were begun almost immediately after birth. Newborns of Michigan mothers who had consumed the highest quantities of PCBs exhibited weaker reflexes and were more likely to be less responsive to visual and auditory stimulation. In North Carolina, weak reflexes and delayed or lack of orientation to stimuli were related to PCB exposure levels at about the time of birth. In the North Carolina group, prenatal exposure to PCBs was associated with poorer psychomotor performance in the first 2 years of

life. PCB exposure levels in the Michigan sample were correlated in a dose-dependent fashion with poorer visual recognition in 7-month old infants. When Michigan children were evaluated at age 4 years, strong associations were found between perinatal PCB exposure and "impaired information-encoding, retention and retrieval."

Hyperactivity, severe mental retardation, and alterations in behavior have been reported with massive exposures--*Yusho* children (whose Japanese mothers were exposed in 1968) and *Yu-cheng* children (whose Taiwanese mothers were exposed in 1979) to PCB-contaminated rice bran oil. Similar findings have been reported in monkeys whose mothers were treated with dioxin.

As is usually the case, PCB and PBB levels in an individual were not always perfectly correlated with the degree of CNS impairment—strongly suggesting a genetic component. Mice and humans are known to exhibit more than 10-fold differences in AHR ligand affinity. It is therefore likely that underlying genetic variability in the ***AHR phenotype*** (the trait being "receptor high *versus* poor affinity") might account for interindividual differences in response to PCB- and PBB-caused CNS toxicity—mediated via either a nongenotoxic signal transduction pathway and/or a genotoxic mechanism. In order to test this hypothesis, one could exploit the known differences in AHR affinity between inbred mouse strains, which have been well characterized during the past 25 years. There also exists the possibility that polyhalogenated biphenyl-induced CNS toxicity might proceed via a phenobarbital receptor-mediated mechanism, which is not at all understood—even in laboratory animals—at the present time.

——Contributed by Daniel W. Nebert and Howard G. Shertzer

Recommended further reading—

Dunckel AE, 1975, An updating of the polybrominated biphenyl disaster in Michigan. ***J Am Vet Med Assn*** **167:** 838-841

Carter LJ, 1976, Michigan's PBB incident: chemical mix-up leads to disaster. ***Science*** **194:** 339-343

Kay K, 1977, Polybrominated biphenyls (PBB) environmental contamination in Michigan, 1973-1976. ***Env Res*** **13:** 74-93

Editorial, 1977, Polybrominated biphenyls, polychlorinated biphenyls, pentachlorophenyl-and all that. ***The Lancet*** **ii:** 19-21

Bekesi JG, Holland JF, Anderson HA, Fischbein AS, Rom W, Wolff MS, Selikoff IJ, 1978, Lymphocyte function of Michigan dairy farmers exposed to polybrominated biphenyls. ***Science*** **199:** 1207-1209

Chen YC, Guo YL, Hsu CC, Rogan WJ, 1992, Cognitive development of Yu-cheng ("oil disease") children prenatally exposed to heat-degraded PCBs. ***J Am Med Assn*** **268:** 3213-3218

Seegal RF, Schantz SL, 1994, Neurochemical and behavioral sequelae of exposure to dioxins and PCBs. *In:* **Dioxins and Health** (Schecter A, ed), Plenum Press: NY, pp 409-447

Jacobson JL, Jacobson SW, 1996, Intellectual impairment in children exposed to polychlorinated biphenyls in utero. ***N Engl J Med*** **335:** 783-789

Faqs about PCBs. ***http://www.io.org/%7Efishenv/faq_pcb/faq_pcb.htm***

Total Immediate Ancestral Longevity (TIAL)

Last August Jeanne Calment died in Arles, France, at the age of 122 years and 164 days—the longest ever documented life of a human. A number of analyses of her and her family tree have appeared in the scientific literature over the past several years. Documenting longevity in 55 of the 62 possible "immediate ancestors" of Ms. Calment (2 parents, 4 grandparents, 8 great-grandparents, 16 great-great-grandparents, 32 great-great-great-grandparents), Robine and Allard [***Science*** **279:** 1834-35, 1998] calculated that Jeanne Calment had a TIAL value [***Hum Biol*** **6:** 98, 1934] of 477, compared with 289 for a "reference family" (living in the same parish over the same time period). Calment's ancestors included 24% who lived to the age of 80 or more, compared with 2% in the control family.

There was no simple hereditary transmission of the longevity trait. The conclusion was that Calment was born into an extraordinary concentration of long-living immediate ancestors, particularly on her paternal side, and that her longevity could be ascribed to living in "an environment perfectly adapted to her genetic profile (and vice versa)."

Mapping New Traits to Chromosomal Sites

Applying the techniques described in ***Interface*** issue #12 ("Correlating a Trait (phenotype) with a Gene(s) (genotype): How Will 'SNPs and DNA Chips' Help Us?"), recent studies have reported**:** a possible gene on Chr 6 that might contribute to IQ [***Science*** **280:** 681, 1998]**;** genes on Chr's 5, 6 & 17 possibly involved in multiple sclerosis [***Am J Human Genet*** **61:** 1379-87, 1997]**;** a gene on Chr 6 apparently associated with severe familial schizophrenia [***Am J Hum Genet*** **61:** 1388-96, 1997]**;** correlation of a particular allele of the angiotensin-converting enzyme (***ACE***) gene with greater physical performance and endurance [***Nature*** **393:**221-22, 1998]**;** possible genes that might contribute to "perfect pitch" (ability of a listener to recognize immediately and correctly the musical note or chord of an auditory tone without benefit of an external reference) [***Am J Hum Genet*** **62:** 221-23; 224-31, 1998; ***Nature Genet*** **18:** 96-97, 1998]**;** a gene on Chr 7 implicated in a severe speech and language disorder [***Nature Genet*** **18:** 168-70, 1998]**;** and a gene on Chr 15 that is presumably linked to severe spelling disability [***Am J Hum Genet*** **63:** 279-82, 1998]. With the help of the Human Genome Project, genetic problems that seemed just a few years ago to be entirely unapproachable are now moving forward with incredible breakneck speed!

Observations by a Biologist

Evolution of weeds on an island

Some creationists might ask "If evolution has really gone on for hundreds of millions of years, prove it. Why can't you show me that it's happening today?" Well, two scientists—comparing the wind-dispersed seeds of a common backyard weed in the daisy family (*Asteraceae*) on islands *versus* the mainland—have demonstrated direct evidence of both the "***founder effect***" (virtually all descendants having arisen from one or a small number of individuals) and rapid evolutionary change.

Cody and Overton studied the "loss of dispersal ability" by plants and animals confined to islands [***J Ecol* 84:** 53-62, 1996]. Many species endemic to remote islands in the ocean lack any obvious means for having reached that island in the first place (*e.g.* trees with fruits intolerant of saltwater and/or too big to be blown by the wind or carried by a bird; also the now-extinct dodo). Cody and Overton examined 240 Canadian Pacific Coast islands—ranging in area from a few square meters to about 1 km². The daisies' parachute-shaped dispersal unit (***diaspore***) contains fluff (the ***pappus***) for wind dispersal and the tiny seed in a capsule (the ***achene***). Obviously, the bigger the fluff ball (V_p) and the lighter the seed (V_a), the longer the parachute is capable of remaining aloft in the wind. By dropping each diaspore in still air from a height of 2 m and measuring the drop time (T_d) before the parachute hits the ground, the scientists found a relationship—*e.g.* T_d is enhanced from 3 to 6 sec as the ratio of V_p/V_a increases from approximately 1,000 to 17,000, implying that such a doubling of drop time would permit the parachutes to be carried twice as far by the wind!

Following 8 summers of study over a 10-year period, these daisies were shown to have smaller parachutes on the islands, as compared with that on the mainland, and population turnover on some islands was found to be rapid—with populations (sometimes just one or a few individuals on one island) often becoming extinct and new ones becoming established. New populations became established after not having existed on that island for as long as the previous 9 years. Thus, Cody and Overton have demonstrated the founder effect over a 10-year period of study**:** among mainland daisies, only those with smaller achenes are more likely to get blown to offshore islands, and achene size then increases with population age so that a population that has remained on an island for about 8 summers has achene sizes no longer significantly different from the daisy achene size on the mainland. Because these weeds are biennials, most of these evolutionary changes are taking place during 5 generations or less!

Gabby Dover (Oxford, England) has called such changes "molecular drive," *i.e.* the changing of genes in an organism over ***x*** generations in response to environmental pressures. Can humans living in Los Angeles County, for example, "adapt" to a heavily smog-pulluted environment such that they become resistant to asthma or watering eyes? And, if so, how many generations would be required to see this adaptation? Answers to these questions are not known, but from this report on daisy parachutes, as well as numerous insecticide-resistance studies and similar experiments, it is anticipated that any species will generally be able to "adapt" (be selected for) after somewhere between five and 40 generations of exposure to a constant environmental pressure!

Idiosyncratic drug reactions

"Idiosyncratic" means, basically, "we don't understand." Undesirable reactions to prescribed and over-the-counter medications kill more than 100,000 Americans and seriously injure an additional 2.1 million, ***each year***. Such reactions—which do not include prescribing errors or drug abuse—rank sixth among U.S. causes of death (behind heart disease, cancer, lung disease, stroke, and accidents). Thirty-nine studies over the past 30 years were summarized in an April 1998 issue of the ***J Am Med Assn***. Such idiosyncratic drug reactions are the manifestation of human pharmacogenetic differences: given the same dose of a particular drug, two individuals respond markedly differently because of their underlying genetic predisposition, *i.e.* genes encoding drug-metabolizing enzymes (DMEs) or receptors controlling DME metabolism are responsible for such dramatic interindividual variability. This field of study has also recently been called "pharmacogenomics" [***Nature Biotechnol* 16:** 492-493, 1998].

LETTERS TO THE EDITOR

RESPONSES/COMMENTS TO VARIOUS QUESTIONS

COMMENT **Pertaining to the last issue's leading article on "arsenic toxicity and cancer" and possible differences (human polymorphisms) in activities of the arsenite methyltransferases (AsMTs), Vasken Aposhian's group at the University of Arizona (Tucson) has begun to study an indigenous population in a small village in Chile who "for thousands of years apparently have been drinking water laced with dangerous levels of arsenic," yet show no signs of cancer. Could it be that their *AsMT* gene(s) encode an enzyme with particularly high activity, *i.e.* enhanced arsenic detoxification?**

COMMENT **Also related to the last issue's leading article—suggesting the existence of human alleles conferring increased resistance to heavy metal toxicity—Ellen Silbergeld (University of Maryland, Baltimore) and coworkers have examined further a genetic epidemiologic study showing a correlation between gold mining areas in Brazil and "malaria hot spots." One common practice in mining is to mix sediments with mercury (Hg) to extract gold-mercury amalgam, then evaporate the Hg to leave the gold behind. Silbergeld's group found blood and urinary Hg levels "more than five times the levels considered to be safe" by the World Health Organization (WHO). Mercury is known to perturb immune functions. Injecting mice with nontoxic doses of Hg, Silbergeld's laboratory demonstrated that Hg lowers the animals' immune defenses against malaria. Could this be why malaria is so prevalent in these Brazilian gold miners? Could other infections such as cholera also be more prevalent in these workers, due to nontoxic levels of Hg? Might interindividual differences (workers with high Hg levels showing no compromised immune functions, workers with low Hg levels having compromised immune functions) be explained by allelic differences in the genes responsible for mercury toxicity or detoxification?**

COMMENT **Pertaining to the *Interface* issue #12's leading article on "single nucleotide polymorphisms (SNPs) and DNA chips," a major article on the large-scale identification of SNPs in the human genome (with David Wang, Eric Lander, and 25 other coauthors in Cambridge MA) has now appeared [*Science* 280: 1077-82, 1998]. Surveying 2.3 million bases (Mb) of DNA by gel-based sequencing plus high-density variation-detection DNA chips, they found 3,241 SNPs, located 2,227 of these on a genetic map, and showed that they could simultaneously genotype 500 of these SNPs. Since all 60,000 to 100,000 human genes are expected to cover roughly 120 Mb, the entire "protein coding region" represents only about 40 times more than this present study!**

On a related subject, Alan Williamson (retired vice president for research strategy, Merck & Co., Inc.) organized a private meeting of drug company executives in April. They concluded that, along with the recent $30 million NIH initiative, the capacity exists in the public and private sector to "create a standard set of about 100,000 informative SNPs in the next 12 to 18 months."

COMMENT **As usual, recombinant DNA methods for "everything!" continue to improve. Remember, one year ago, Dolly the cloned sheep was the successful result of 1 out of 247 adult cells attempted to be cloned. Recently, transgenic calves were cloned: actively dividing fetal fibroblasts were modified with a marker gene, a clonal line was selected, and the cells were fused to enucleated mature oocytes. Out of 28 embryos transferred to 11 recipient cows, three healthy identical transgenic calves were produced [Science 280: 1256-59, 1998]. Pushing a 10% success rate now is definitely profitable.**

Q **A friend of mine recently predicted that "proteomics is going to become a bigger and more important thing than genomics." What, exactly, is *proteomics*? And, will it ever really replace the advances in genomics and pharmacogenomics research that are expected to occur in the next decade?**

A First introduced in July 1995, the term ***proteomics*** *was defined as the "total protein complement of a genome." In DNA there are active genes (turned "on" at all times), pseudogenes (appearing like a gene but never producing a functional protein), inducible genes (turned on only during development, in a specific tissue or cell type, or in response to a particular endogenous or foreign stimulus), and intergenic spacer regions (95%+ of the genome). There are also many examples of the "levels of transcripts" (messenger RNA) that do not correspond to the "levels of functional protein." Proteins can also be posttranslationally modified (e.g. glycosylation, acetylation, phosphorylation, ubiquitinization, etc) to become "active" or "inactive" in function. Two-dimensional electrophoresis can now resolve a cell into about 10,000 reproducible spots representing individual distinct peptides and proteins. Just as with DNA chips, "protein microarray" techniques are constantly being improved—so that protein concentrations in the attomole (10^{-18} mole) range can be quantitated, sequenced, and determined to be increased or decreased in a particular cell type, or during development, or in a disease process. Proteomics will never "replace" genomics, but data obtained from protein microarrays will certainly complement gene sequence data.* ***Pharmacogenomics*** *(developing new drugs based on knowledge of a newly discovered gene) and* ***proteomics*** *(determining the enhanced or diminished levels of a specific protein in some signal tranduction cascade) are both here to stay!*

Second Largest Gene Known

A Japanese research team in Tokyo has identified and characterized a very large gene, which they have called ***parkin***, whose mutated version causes a rare inherited form of Parkinson's disease—"autosomal recessive juvenile parkinsonism" (AR-JP). Parkinson patients are unable to keep their hands from trembling and unable to relax their face to form a smile.

Located on the long arm of chromosome 6, the gene has more than 500,000 base pairs**;** only the human ***dystrophin*** gene, involved in muscular dystrophy, is larger. The researchers speculate that the cell with abnormal parkin protein may accumulate toxic levels of proteins because of a defect in the normal protein-degrading machinery within the cell.

Whose DNA Is It, Anyway?

Working with indigenous, or formerly genetically isolated, populations can lead to important inroads into characterizing and understanding various human diseases. Some small populations go through a ***genetic bottleneck*** (few people able to breed) due to malnutrition, disease or other hardship. Other isolated groups simply display a "***founder effect***" (virtually all descendants having arisen from one or a small number of individuals). Working with such populations has become an increasingly popular approach with healthcare-oriented companies.

Sequana (now part of AxyS, San Diego, CA) discovered a putative gene for asthma 2 years ago by working with the population of Tristan da Cunha, a tiny island halfway between South Africa and South America. AMRAD (Melbourne) made an announcement in January 1998 that it would study Tasmanians for the possible development of new drugs for osteoporosis, endometriosis, and multiple sclerosis. Eurona Medical (Uppsala, Sweden) has access to 3 million patient samples—claimed to be the largest clinical archives—and plans to study hypertension, cancer and central nervous system disorders. Genset (Paris) is collecting North African DNA samples in order to investigate diseases relevant to populations living in that area. The latest is DeCODE Genetics (Reykjavik, Iceland), in collaboration with Hoffmann-La Roche (Basel, Switzerland), which wants to use the entire population of Iceland to study "12 common neurological, cardiovascular, and metabolic diseases including schizophrenia, manic depression, adult-onset diabetes, and Alzheimer disease"**;** along with the $200 million deal came the stipulation that the Swiss company would donate to the Icelandic population, free of charge, all medications resulting from the collaboration. At the moment, the bill in the Icelandic Parliament has been blocked pending further study [***Nature Biotechnol*** **16:** 496, 1998].

Is it ethical and reasonable for a company to "own" the DNA of an entire indigenous population? Harboring back to the ethical dilemmas discussed in ***Interface*** issue #10, more of these "medical genetics" problems appear to be surfacing with each passing month.

Enhanced Male Fitness

Please check out Bill Rice's article, "Male fitness increases when females are eliminated from the gene pool: Implications for the Y chromosome" [***Proc Natl Acad Sci USA*** **95:** 6217-21, 1998]. This subject appears to support the concept of male-only health spas.

"The Venter Venture"

The Human Genome Project (HGP), which began 1 Oct 1990, had planned to complete the sequencing of the 3 billion base pairs (bp) in the human genome by the end of 2005—at an estimated cost of $3 billion. This was to be done with no more than one mistake per 10,000 bp and no gaps in the sequence data. During this past year, it has been discussed whether the HGP or other organizations such as the ***Environmental Genome Project*** should be responsible for delineating polymorphisms in disease-related genes (*i.e.* looking at allelic frequencies in large human populations)**;** this topic has been discussed several times in the ***Interface*** from issue #10 to the present.

Well, the HGP and Francis Collins (Director, National Human Genome Research Institute, NHGRI) received a major jolt this spring, with rumblings still going on this summer. ***J. Craig Venter***, president of The Institute for Genomic Research (TIGR) in Rockville MD, announced May 9th that he and the Perkin-Elmer Corp. (Norwalk CT) plan to form a new company that would "substantially complete the sequence of the entire human genome in 3 years" at a cost of perhaps as little as $300 million [Venter et al., ***Science*** **280:** 1540-42, 1988]. The proposal, therefore, is to get the job done in less than half the time (between now and 2005) at a cost of about one-tenth that of the federally funded project!

Scientifically, the method proposed is the standard "shotgun approach" used by many of us more than 15 years ago but, of course, on a much more grandiose scale. First, they propose to use 230 of the latest Perkin-Elmer sequencing machines—which are capable (high-through-put microcapillary electrophoresis) of sequencing *100 million bp* per day, 7 days a week. Theoretically, complete contiguity of "shotgun clones" should be achieved by about nine times more DNA than just one genome. Venter proposes 46X coverage, meaning that some pieces of DNA (contigs) might be sequenced 40 times or more. Still, he expects 99% of the genome to be completed within one year**;** the following 2 years will be spent fitting the contigs together and filling in key gaps. When completed, there will still be "an estimated 2000-5000 gaps of about 58 bp each" on average**;** these would be regarded as "too expensive to close" and would be left to the research community "to do, as needed." And—for a warm-up and to prove feasibility of this project—Venter plans to collaborate with Gerald Rubin (Univ. of California, Berkeley) to sequence the entire genome of the fruit fly *Drosophila melanogaster* genome (120 million bases, Mb) before the end of 1999!

Since the Venter/Perkin-Elmer project will be looking at multiple individuals (number not yet decided upon), they also plan to characterize (and patent?) an unspecified number of single nucleotide polymorphisms (SNPs, see ***Interface*** issue #12) and "patent maybe only 200 to 300 genes of disease interest." This "quick-and-dirty" approach reinforces the concern of federally-funded scientists about aggressive scientific entrepeneurs—presumably collaboration with the publically funded community would be more profitable than trying to compete or simply being hostile? All this led to a hastily drawn meeting in early June in Virginia, at which time the NHGRI proposed a 5-year plan (to be finalized by October 1998) calling for a 10-fold increase in DNA sequencing, or the generation of 500 Mb of sequence per year, by 2003. Stay tuned...!!

SCIENCE LITE

Medical Terminology for the Layman

We try in this NewsLetter to explain each scientific term for our nonscientist readers. Here, in alphabetical order, are some some further medical terms simplified.

- ***Artery*** – The study of fine paintings
- ***Barium*** – What you do with the body after CPR has failed
- ***Benign*** – What you be, after you be eight
- ***Caesarean section*** – A district in Rome
- ***Colic*** – A sheep dog (*e.g.* Lassie)
- ***Coma*** – One kind of punctuation mark
- ***Congenital*** – friendly
- ***Dilate*** – to live long
- ***Fester*** – Quicker
- ***GI Series*** – Baseball game between teams of soldiers
- ***Grippe*** - A suitcase
- ***Hangnail*** –Something on the wall for coats and other things
- ***Medical staff*** – A doctor's cane
- ***Minor operation*** – Digging for coal, copper, uranium, etc.
- ***Morbidity*** – The act of making a higher offer
- ***Nitrate*** – Lower than the day rate
- ***Node*** – Was aware of
- ***Organic*** – Musician who often plays in church
- ***Outpatient*** – Person who has fainted
- ***Post-operative*** – A letter carrier
- ***Protein*** – Being in favor of young people between the ages of 13 and 19
- ***Secretion*** – The act of hiding anything
- ***Serology*** – The study of English knighthood
- ***Tablet*** – A small table
- ***Tumor*** – An extra pair
- ***Urine*** – Opposite of "you're out"
- ***Varicose veins*** – Veins that are very near one another

Modified from Allquotes iv.v (journal)(rogerb@microscoft.com)

COEP
Community Outreach and Education Program

The Community Outreach and Education Program Core welcomes the new COEP Program Manager, **Susan Vandale**, hired in March 1998. **Dr. Vandale** holds a Ph.D. in Health Education from the School of Public Health, University of North Carolina. She has been a leader in health education and health services research projects in Laredo, Texas, and Mexico City. She has published extensively in scientific journals in the U.S. and Latin America. As COEP Program Manager, **Vandale**'s efforts will include the development of a LEGENDS (Learning Exchange for Genetic and Environmental Disease Solutions) adult-geared curriculum designed to promote public understanding and discussion concerning new genetic technology and gene/environment interactions in disease. The first LEGENDS activity is a 5-day workshop, to be piloted with a group of health professionals later this year. The course covers environmental health, genetics, toxicology, epidemiology, and environmental/genetic disease case studies. A laboratory manual and an instructor's manual are being prepared. The expertise of **CEG** members will be invaluable in helping LEGENDS with content, review and presentation of the course.

Congratulations to the 1998 CEG Pilot Project Awardees!

Michael P. Carty, PhD, (Environmental Health)
"Complementation of the UV-sensitive phenotype of human Xeroderma Pigmentosum variant cells by genes from the *RAD6* epistasis group of *Saccharomyces cerevisiae*"

William D Hardie, MD, (Pediatrics)
"Role of transforming growth factor α and the epidermal growth factor receptor in protection from oxidative lung injury"

Jun Ma, PhD, (Pediatrics)
"Genetic studies of heavy metal toxicity in yeast"

Dan Nebert, MD, (Environmental Health)
"Effect of polybrominated biphenyls (PBBs) on behavior"

Susan Pinney, PhD, (Environmental Health)
"Genetic epidemiology of lung cancer"

James M. Stark MD, PhD, (Pediatrics)
"Genetic analysis of RSV infection in a mouse model"

John C. Winkelmann, MD, (Int Med-Hemat/Oncol)
"Genetic and environmental factors producing increased colorectal cancer and polyps in Russian Jewish immigrants in Cincinnati"

CEG - SPONSORED SPEAKERS

Michael Karin, MD
Professor, Department of Pharmacology
School of Medicine, University of California at San Diego
La Jolla, California
1 April 1998 ***"Signaling pathways that mediate responses to environmental Stress"***
2 April 1998 ***"The JNK kinase cascade and programmed cell death"***

Jack Taylor, MD, PhD
Head, Molecular and Genetic Epidemiology Section
NIEHS, Research Triangle Park, North Carolina
22 April 1998 ***"Epidemiologic studies of gene-environmental interactions"***

Allan B. Okey, PhD
Professor and Chair, Department of Pharmacology
University of Toronto, Ontario Canada
29 April 1998 ***"Human AH receptor and variations in responses to dioxins"***

Ranajit Chakraborty, PhD
Allen King Professor of Biological Sciences
Human Genetics Center
University of Texas Health Science Center, Houston, Texas
6 May 1998 ***"Human genome diversity: Some experiences from DNA polymorphisms"***
7 May 1998 ***"Risk estimates for ionizing radiation: Effects of genetic heterogeneity"***

CEG Members in the News

Eula Bingham and **Glenn Talaska** were intived participants in a roundtable discussion at the American Industrial Hygiene Conference on "The Impact of the Human Genome Project on Biological Monitoring: Safer Workers or Brave New Workplace" (May 1998, Atlanta, Georga). Bingham chaired the roundtable and provided the Introduction. Talaska's presentation was entitled ***"The impact of N-acetyltransferase on human genotoxic response to prevent discrimination and maintain privacy and confidentiality"***

Ranjan Deka was invited to speak at the EMBO (European Molecular Biology Organization) workshop on "Trinucleotide Expansion Diseases in the Context of Microsatellite and Minisatellite Evolution" held at the MRC Clinical Center (April 1998, Imperial College, London, England). He presented a talk entitled ***"Rate and directionality of mutations at trinucleotide repeats."*** He also received a 4-year R01 grant for $1,456,405 from the NIH for a study entitled "Genome scan for NIDDM susceptibility genes among Samoans."

Tom Doetschman delivered an invited seminar in the Cell Biology Department, Vanderbilt University (April 1998, Nashville, Tennessee) and also was invited to deliver a talk on ***"FGF2 in vascular tone and response injury"*** at the "Vascular Cell Biology, Genetic Approaches" session of the Gordon Conference at Plymouth State College (June 1998, Plymouth, New Hampshire).

George Leikauf was invited to speak on ***"Mechanisms of environmental lung injury"*** at the "Indoor Air Quality All-Ohio Safety and Health Congress and Exhibit" (March 1998, Cincinnati, Ohio). He was also a featured speaker at the American Thoracic Society International Conference on "Respiratory Disease: Mechanisms Mini-symposium" (April 1998, Chicago, Illinois). He also chaired a session at the Thoracic Society International Conference (April 1998, Chicago, Illinois) delivering a talk entitled ***"The genetics of bronchial hyperreactivity."*** At the National Institute of Occupational Safety and Health, conference on "Occupational Asthma: In and Out of the Workplace (May 1998, Morgantown, West Virginia) he delivered an invited seminar on the subject of ***"Genetic determinants of irritant-induced airway responses."*** He was also a featured speaker at the American Association for Aerosol Research, with a talk entitled ***"Pathogenetics of particulate matter"*** (June 1998, Cincinnati, Ohio).

Grace Lemasters, Tatiana Foroud, Rakesh Shukla and other members of the Genetic Epidemiology and Biostatistics F&S Core successfully presented their second Workshop, entitled "QTL Mapping in Animal Models" (May 1998). Featured speakers included Beth Bennett, PhD (University of Colorado) who addressed ***"What are recombinant inbreds, inbred and outbreds; What are their differences, How can they be used to map genes? What are congenics, speed congenics;*** and ***How to select a good animal model."*** Howard J. Jacob, PhD, (Medical College of Wisconsin) then spoke about ***"Marker development; Results from recent mapping work;*** and ***Approaches to finding the QTL."*** As with Workshop #1, Workshop #2 is available on VHS for viewing by contacting grace.lemasters@uc.edu.

Dan Nebert accepted an invitation to become a member of the External Advisory Board, Howard University Cancer Center (Lucile L. Adams-Campbell, Director), Howard University Medical Center, Washington DC**;** Dan was elected this spring to receive the ***University of Cincinnati 1998 Distinguished Research Professorship Award***, "the highest honor this university has to bestow, for recognition of excellence in research." He was also an invited speaker at the Second Annual Workshop on "Transgenic Model Systems and Molecular Toxicology," National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina (April 1998), and at the session on "Transgenic Animals to Predict Drug Metabolism," during the 12th International Symposium on Microsomes and Drug Oxidations (July 1998, Montpellier, France).

Peter Stambrook was elected to the Council of the Environment of the Environmental Mutagen Society, and also is organizing a symposium on chromosome architecture and function relating to chromosomal stability for the next Electron Microscope Society's annual meeting (March 1999).

David Warshawsky organized a symposium entitled "Polycyclic Aromatic Hydrocarbons (PAH) in Carcinogenesis" at the IIIrd International Congress of Pathophysiology (June-July 1998, Lathi, Finland) where he also delivered a lecture on the ***"Metabolic activation of polycyclic and N-heterocyclic aromatic hydrocarbons."*** Seven lectures were given by reseachers in the field of PAH mixtures: ranging from sources, DNA adduction and oncogene activation, biological effects, and mechanistic studies of synthetic and field PAH mixtures, to risk assessment of mixtures.

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, **Marshall Anderson, PhD, Director**

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Welcome to new CEG members

The CEG has three new members:

Bruce J. Aronow, PhD
Associate Professor of Pediatrics
Division of Molecular Developmental Biology
Children's Hospital Medical Center
University of Cincinnati
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http://www.uc.edu/~aronowbj
Research in Aronow's laboratory is directed to understanding how genes are activated from mammalian chromosomes. The general problem that he is addressing is to determine the genetic codes that allow mammalian genes to overcome the repressive effects of high density chromatin packing.

Michelle Barton, PhD
Assistant Professor of Molecular Genetics
University of Cincinnati, College of Medicine
http://www.molgen.uc.edu/cv/Barton/Barton.html
michelle.barton@uc.edu
Barton's interests include reconstitution of gene regulation using chromatin and synthetic nuclei templates. The model system being studied is the activation of α–fetoprotein gene expression during development, hepatocellular carcinogenesis, and liver regeneration.

Jeffrey Molkentin, PhD
Assistant Professor of Pediatrics,
Molecular Cardiovascular Biology
Children's Hospital Medical Center
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Molkentin's interests are in the intracellular signaling pathways and transcriptional regulatory pathways that direct cardiac hypertrophy and disease. Specifically, his laboratory is investigating the role that the calcium-regulated phosphatase calcineurin plays in cardiac pathology.

Personals:

Very selective oligonucleotide seeks right target for long-term hybridization.