



INTERFACE: GENES AND THE ENVIRONMENT

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“Multiple Chemical Sensitivities Syndrome” (MCSS): What Is It, and What Is Known about It?

Since its beginning in 1994, *Interface* has always encouraged readers to contact us (letter, fax, email, telephone) about *any* question or comment they might have, whatsoever, concerning “the *interaction of genes with our environment.*” These questions and comments can reflect global concerns, political issues, response to an article in *Interface*, something they’ve heard or read about in the media, or personal medical questions about themselves or friends or family members. If we categorize or classify the “subjects,” or topics asked about over the years, the overwhelming majority would be in the area of *multiple chemical sensitivities syndrome* (MCSS)—of the person contacting us or a friend or relative of that person.

What is MCSS?

Actually, the preferred medical term is *Idiopathic Environmental Intolerance* (IEI), which can be defined as a “chronic, recurring disease caused by a person’s inability to tolerate an environmental chemical or class of foreign chemicals.” *Idiopathic* simply means “the cause of this disease is not known.”

IEI thus represents a complex gene-environment interaction, the true cause of which is currently unknown. There is almost always a precipitating event, usually associated with the smell of a chemical, and a response involving one or more organ systems. Once the initiating event has passed, the same response or even an exaggerated response occurs each time the stimulus is encountered again. Often the initiating stimulus is a higher dose or an overwhelming dose, but subsequently much lower doses can trigger the symptoms. A number of unrelated chemicals (*e.g.* insecticides, antiseptic cleaning agents) might precipitate the same response. Because the syndrome is similar to certain allergic conditions and to certain organ-system responses caused by emotional disturbances, IEI has often been confused with allergy (*atopy*) or psychiatric illness. Disagreement among physicians and medical researchers—as to what IEI really is—has, of course, made research funding difficult (“is this a *real* syndrome, or is this a mental problem or a simple allergy?”). In fact, in a environmental health sciences meeting in Brisbane, Australia, several years ago, there was an old-fashioned debate on MCSS, and the proponents who believed that it was simply a psychiatric disorder won the debate!

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Six criteria of IEI

Several years ago a committee of experts in this field decided upon a consensus as to what “qualifies” the patient as truly having IEI [*Arch Environ Health* 1999; **54**:147]. Six criteria were decided upon:

1. Symptoms are reproducible with repeated (chemical) exposures.
2. The condition is chronic.
3. Low levels of exposure (lower than previously or commonly tolerated) result in manifestations of the syndrome (*i.e.* increased sensitivity).
4. The symptoms improve, or resolve completely, when the triggering chemicals are removed.
5. Responses often occur to multiple chemically-unrelated substances.
6. Symptoms involve multiple-organ symptoms (runny nose, itchy eyes, headache, scratchy throat, ear ache, scalp pain, mental confusion or sleepiness, palpitations of the heart, upset stomach, nausea and/or diarrhea, abdominal cramping, aching joints).

Several medical conditions appear to be related to, or overlap with, IEI—such as sick-building syndrome (SBS), food intolerance syndrome (FIS), and perhaps the Gulf War Illness (GWI). In each of these, a chemical (smell usually, or taste) appears to precipitate one or more organ-system responses. The initiating culprit might be: chemicals in a new rug, cockroach dander, or freon circulating in a closed-ventilation building (SBS); chemicals in wine, processed corn products, or sulfites consumed (FIS); or nerve gas, organophosphates, or pesticides used by soldiers during the brief 1991 war in the Middle East (GWI). Additional conditions (of discomfort, pain or dysfunction) that might have a genetic component but also seem to have an environmental stimulus include: chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, atypical connective tissue disease after silicone breast implants, chronic *hypoglycemia* (low blood sugar), drug-induced autoantibodies/*hepatitis* (liver toxicity), illness while living near a toxic waste dump site, dental amalgam disease, and MTBE (methyl-*tert*-butyl ether, a gasoline additive)-associated symptoms. Inflammation of the lungs caused by diesel exhaust particles (DEPs) is of particular interest, since it illustrates the potential for the drug biotransformation and immune systems (which protect us from small and large foreign compounds, respectively) to interact and contribute to the disease process. In this situation, cellular processes regulated by the aryl hydrocarbon receptor (AHR) apparently activate an inflammatory response

involving TH2 helper, subsequently increasing immunoglobulin E (IgE) production.

How might we dissect this complex disease?

Frequently, individuals with IEI present with symptoms of *rhinitis* (runny nose), along with other diffuse systemic complaints. First, the physician must determine whether the patient has a runny nose due to an allergy problem (*allergic rhinitis*) or not an allergy problem (*nonallergic rhinitis*).

Seasonal allergic rhinitis refers to patients with allergy symptoms triggered by pollen or mold-spore allergens. “Triggering stimuli” occur when the patient is outdoors during the pollen seasons. Symptoms can include sneezing fits (*i.e.* 5-10 sneezes in succession), itching of the eyes/ears/nose/throat/roof of the mouth, runny nose, watery/puffy eyes, nasal stuffiness, post-nasal drip, sinus pressure, and fatigue. *Perennial allergic rhinitis* refers to year-round hay fever symptoms that are triggered by indoor allergens such as dust mites, cockroaches, mold-spores, feathers, and animal dander. Perennial allergens may be difficult to identify by history alone; skin testing is necessary to confirm sensitization to these allergens but does not indicate that the individual is currently being exposed.

A patient with *nonallergic rhinitis* is one who has had an allergic component ruled out by skin tests. Nonallergic rhinitis can be further divided into *inflammatory* (nonallergic rhinitis with eosinophilic syndrome, NARES) and *noninflammatory* (vasomotor rhinitis, VMR) subtypes. Nonallergic rhinitis is an organ-specific disorder of *unknown etiology* (cause not understood) that is aggravated by strange chemical smells and weather changes. The noninflammatory form of nonallergic rhinitis, VMR, satisfies the first five of the above criteria, suggesting that this disorder is a potential model [*Ann Allergy Asthma Immunol* 2001; **86**:494] for investigating the genetic etiology of the more global disease, IEI.

Nonallergic VMR can mimic allergic rhinitis. Patients with nonallergic VMR experience nasal congestion, postnasal drip, headaches/sinus pressure and ear-plugging. Skin testing to seasonal and perennial allergens is negative (*i.e. non-atopic*). “Triggering stimuli” for nonallergic VMR include weather changes (temperature or barometric pressure changes), postural changes, and irritants such as smoke, perfumes, potpourris, solvents, cleaning agents, incense, and soaps and detergents (to name a few).

Is IEI associated with mutations in olfactory receptor (OR) genes?

The field of *olfaction* (ability to smell distinct classes of things) has recently exploded with the advent of genomics and the Human Genome Project. A superfamily of ~1000 odorant receptor (*OR*) genes (63% pseudogenes) has been discovered, located in multiple clusters on all but two of the 24 human chromosomes (22 autosomes, X, Y chromosome). These *OR* clusters comprise 17 gene families, four of which contain >100 members each [*Genome Res* 2001; **11**:685]. Interestingly, 63% of the human's *OR* genes are nonfunctional (*pseudogenes*). The fact that apes have a greater percentage of functional *OR* genes and rodents have a much, much greater percentage of functional *OR* genes—is strong evidence that the evolving human species has lost its need for maintaining a very keen sense of smell. The *OR* gene superfamily comprises 1-3% of the entire genomic complement of genes, and is likely to be the largest gene superfamily in the genome of any species.

Other clusters of human chemosensory genes include the vomeronasal receptors, related to an accessory olfactory organ thought to be largely inactive in primates. The *OR* genes are members of the 7-transmembrane domain G-protein-coupled receptor (*GPCR*) superfamily. *In situ* hybridization studies indicate that each *OR* gene is expressed in ~1 per 1000 olfactory epithelial (OE) neurons, suggesting that each OE neuron expresses only one *OR* gene [*Cell* 2000; **100**:611]. People clearly have very different abilities to sense smells. Polymorphisms in many of these genes have been reported, implying a mechanism for interindividual variation in olfactory responses [*Gene* 2000; **260**:87]—and perhaps to diseases triggered by olfactory stimuli.

Conclusions

IEI is a complex disease involving gene-environment interactions [*Environ Health Perspect* 2000; **108**:1219]. Perhaps one place to begin, in dissecting this complex disease, would be to study nonallergic VMR because it can be more precisely defined. Would polymorphisms, in particular functional *OR* genes, be responsible for nonallergic VMR? Could nonallergic VMR be a sufficient phenotypic end-point such that it could be examined in a phenotype-genotype association study involving a candidate-gene approach, a candidate-gene-region approach, or a total genome scan?

It seems tempting to postulate that nonallergic VMR might be a sufficiently quantitative trait that it

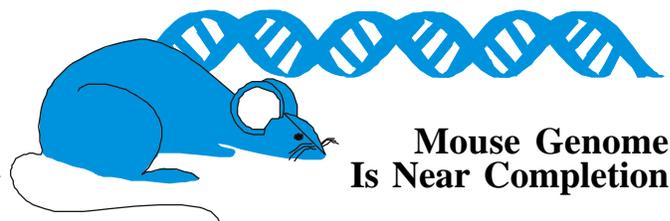
can be used first in attempting to dissect the very complex disease syndromes associated with IEI, SBS, FIS and GWI. Anyway, this is the approach that is being taken by three University of Cincinnati CEG researchers—Jonathan Bernstein, Dan Nebert, and Li (Felix) Jin. Given the exploding advances in our knowledge about the human genome, it seems that the time to tackle this complicated (and very common) environmental disease is **now**.

—Contributed by Dan Nebert, with help from Steve Leeder, and Jonathan Bernstein.



Pollution Monitoring at the World Trade Center

Environmental health centers at Columbia University, Mount Sinai School of Medicine, New York University, and Johns Hopkins University are participating with officials at the National Institute of Environmental Health Sciences (NIEHS), U.S. Environmental Protection Agency (EPA), and Centers for Disease Control and Prevention (CDC) to move swiftly—but discreetly—on collecting early exposure data on the possible fallout from collapse of the World Trade Center. Early monitoring of levels of various heavy metals and asbestos will be important in assessing the health of the rescue workers later [*Nature* 2001; **413**: 335].



Mouse Genome Is Near Completion

At the Mouse Molecular Genetics Meeting (August 2001) held in Heidelberg, Germany, Celera announced it had completed ~98% of the mouse genome from three different inbred strains—129X1/sV, A/J and DBA/2J—and nearly 50% of this has been assembled into scaffolds of more than 5 million bases (Mb) each. These data will complement the federal government-sponsored sequencing of the genome of the C57BL/6J inbred mouse strain.

Latest Findings on Evolution

What follows is a synopsis of some of the more interesting things that have happened during the last 6 months of 2001 with the Human Genome Project (HGP), and related *evolution*-related news, provided chronologically:

Jul 2001 (or earlier) Studies over the past decade [*Science* 2001; **292**:627] have always shown that chimpanzees, gorillas and orangutans have 3-4 times more DNA variant sites in their maternally inherited mitochondrial DNA (mtDNA) than humans. This appears to be strong evidence for a *genetic bottleneck* during human evolution, when a population of perhaps less than 10,000 survivors (between 110,000 and 60,000 years ago) gave rise to all modern humans. Looking at the Y chromosome in 12,127 males from 163 populations of East Asians, Li Jin and colleagues [*Science* 2001; **292**:1151] found *not even one exception* to the common finding that *all* had originated in Africa between 89,000 and 35,000 years ago. This finding indicates that modern humans of African origin completely replaced any earlier populations in East Asia!

A team of Kenyan and French anthropologists found fossil remains of a previously unrecognized genus and species of human ancestor [*Nature* 2001; **410**:527], which has now been named *Orrorin tugenensis* (named after the Tugen Hills). This newly described ancestor appears to be on the direct line leading to modern humans. The volcanic materials, in which the fossils were found, has been very definitively radiologically dated to 6.2 to 5.6 million years before the present (YBP). The date at which the great apes had diverged from the human ancestor had generally been agreed upon to be ~5 million YBP, but now obviously it must be pushed further back in time. It is becoming more and more clear that modern human (*Homo sapiens sapiens*) evolved during a number of fits and starts—numerous fossils providing evidence for sublines, which began to evolve but then failed somewhere along the way (**Figure 1**).

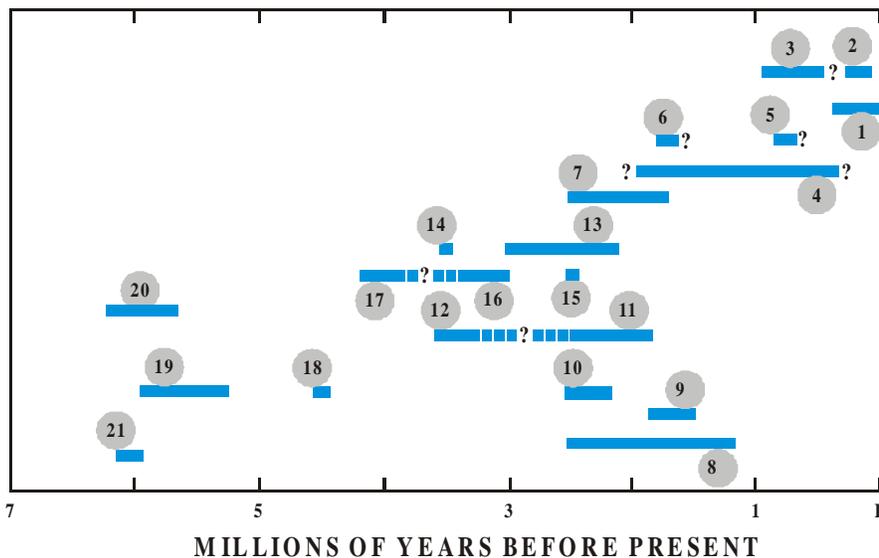


Figure 1. Different lines of humans (Hominids) during more than 6 million years of evolution. **1**, *Homo sapiens sapiens*. **2**, *H. neanderthalensis*. **3**, *H. heidelbergensis*. **4**, *H. erectus*. **5**, *H. antecessor*. **6**, *H. ergaster*. **7**, *H. habilis*. **8**, *Paranthropus boisei*. **9**, *P. robustus*. **10**, *P. aethiopicus*. **11**, *Kenyanthropus rudolfensis*. **12**, *K. platyops*. **13**, *Australopithecus africanus*. **14**, *A. bahrelghazali*. **15**, *A. garhi*. **16**, *A. aferensis* (“Lucy”). **17**, *A. anamensis*. **18**, *Ardipithecus ramidus ramidus*. **19**, *A. ramidus kadabba*. **20**, *Orrorin tugenensis*. **21**, *Sahelanthropus tchadensis* (Toumai). P, present day.

Afrotheria is an intriguing hypothesis combining geology with genomics [*Proc Natl Acad Sci USA* 2001; **98**:1]. Evidence has emerged during the past 3 years that one-third of the orders of placental mammals form an ancient group that evolved on Africa—when that continent was isolated from others because of plate tectonics. This super-order contains six orders: elephants, sea cows, hyraxes, armadillo, elephant shrews, and golden moles.

An earlier issue of *Interface* described the complete sequencing of the *Arabidopsis thaliana* genome, and we’ve also described the phenomenon of “horizontal gene transfer” whereby genes of one organism are captured by another. It now appears [*Trends Genet* 2001; **17**:113] that, of the 25,000 or more nuclear genes in this tiny mustard plant, between 400 and 2200 of them seem to have originated in cyanobacteria! Further, there

is the claim [*Nature* 2001; **409**:860; *Trends Genet* 2001 **17**:235] that 113 genes in the human genome have bacterial origins!

Aug 2001 *Epigenetics* is defined as processes that regulate gene expression, and even inheritance, that are controlled by means other than classical Mendelian genetics. How did epigenetic regulation arise? For the case of DNA methylation, imprinting, RNA-mediated silencing—there is growing evidence [*Science* **293**, special topic issue of 10 Aug 01] that these mechanisms evolved as part of a host-defense mechanism against virus and parasitic DNA.

Sep 2001 During the past decade, evidence has been growing that the marine mammal *cetaceans* (whale, porpoise and dolphin) are more closely related to hoofed mammals (*ungulates*) that include cow, hippopotamus, pig, camel and giraffe than any other group of mammals. Partial fossil skeletons now have shown for the first time [*Nature* 2001; **413**:277] that whales were fully land-animals and were even efficient runners.

In addition to changing global ecology, human population growth and biotechnology also have affected evolutionary trajectories—dramatically accelerating changes in other species [*Science* 2001; **293**:1786]. Examples include antibiotic and HIV resistance to drugs, plant and insect resistance to pesticides, rapid changes in invasive species, life-history changes in commercial fisheries, and pest adaptation to bio-engineering products. This accelerated evolution costs at least \$33 billion to \$50 billion a year in the U.S. alone.

Nov 2001 At the Symposium on Evolutionary Genomics (Nov 2001, Atami, Japan), it was concluded that we now have complete genome sequences of ~70 bacterial species, and of six eukaryote multicellular species (fly, worm, mustard plant, human, rice, mouse), that are either complete or almost complete [*Trends Genet* 2002; **18**:239]. Numerous topics discussed at this meeting included: the unexpected discovery of large numbers of pseudogenes (including bits and pieces of one or a few exons near a functional gene), comparisons of closely related organisms to understand developmental biology/evolution better, co-evolution of interacting proteins (or interacting organisms), and comparative genomics of the human and apes (to understand why humans have advanced so much more rapidly than apes during the past 5 million years).

Observations by a Biologist

Why do we have autumn leaves?

Why would trees want to make large amounts of costly compounds in their leaves just before shedding them? Hamilton and Brown [*Proc R Soc Lond B* 2001; **268**: 1489] surveyed 262 tree species and found that the yellowness or redness of a tree's autumn leaves was correlated with the number of aphids that attack it. Maples, which put on some of the most spectacular displays, are the most heavily aphid-infected species—consistent with the idea that tree species invest more in color signaling if they are under attack. So, the trees are sending the message “Go pick on someone else” to their insect enemies. This is an intriguing idea. But, will it hold up, if one looks beyond aphids? Also, the amount of color varies greatly between one species of tree (discussed in an earlier issue of *Inter-face*); will the more colorful ones within the species have more aphids harrasing them than the less colorful ones of the same species?

**The problem with
the gene pool is that
there is no life guard**

from Fax News Nov 5, 2001

SCIENCE LITE

Adagio fromaggio: To play in a slow and cheesy manner.

AnDante: A musical composition that is infernally slow.

Antiphonal: Referring to the prohibition of cell phones in the concert hall.

A patella: Unaccompanied knee-slapping.

Bar line: What musicians form after a concert.

Basso continuo: The act of game fishing after the legal season has ended.

Basso profundo: An opera about deep sea fishing.

Brake drum: The instrument most used to slow the tempo in an orchestra.

Concerto grosso: A really bad performance.

Coral Symphony: (see: Beethoven -- Caribbean period).

D.C. al capone: You betta go back to the beginning, capiche?

Dill piccolo: A wind instrument that plays only sour notes.

Diminuendo: The process of quieting a rumor in the orchestra pit.

Eardrum: A teeny, tiny tympani.

Fermantra: A note that is held over and over and over and...

Fermoota: A rest of indefinite length and dubious value.

Fiddler crabs: Grumpy string players.

Flute flies: Gnat-like bugs that bother musicians playing out-of-doors.

Fog horn: A brass instrument that plays when the conductor's intentions are not clear.

Frugalhorn: A sensible, inexpensive brass instrument.

Gaul blatter: A French horn player.

Good conductor: A person who can give an electrifying performance.

Gregorian champ: Monk who can hold a note the longest.

Kvetchendo: Gradually getting annoyingly louder.

Mallade: A romantic song that's pretty awful.

Molto bolto: Head straight for the ending, but don't make it seem rushed.

Opera buffa: Musical stage production at a nudist camp.

Pipe smoker: An extremely virtuosic organist.

Poochini: When playing or singing, to be accompanied by your dog.

Pre-Classical Conservatism: "if it ain't baroque, don't fix it".

Status cymbal: An instrument to be played at inaugurations and socialite balls.

Tempo tantrum: What a young orchestra is having when it's not keeping time with the conductor.

Timpani Alley: A row of kettledrums.

Vesuvioso: A gradual buildup to a fiery conclusion.

The most exciting phrase to hear in science, the one that heralds new discoveries, is not "Eureka... I have found it,!" but "That's funny..."
..... Isaac Asimov

LIFE ALWAYS GIVES YOU BACK WHAT YOU GIVE OUT. YOUR LIFE IS NOT A COINCIDENCE, BUT A MIRROR OF YOUR OWN DOINGS.....Author Unknown

“ lead us not into temptation and deliver us from e-mail”

Latest in Genetics and Genomics, ...

What follows is a synopsis of some of the more interesting things that happened during the last 6 months of 2001 with the Human Genome Project (HGP), and related genetics/genomics news, provided chronologically:

Jul 2001 A new public-private consortium (including the Sanger Centre in Britain and the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts) plans to map genetic variation across the entire human genome [*Nature* 2001; **412**: 106]. The proposed \$60-million project plans to make a publicly available genetic map of ~300,000 haplotypes within 2 years. *Haplotypes* represent “the patterns of co-occurrence of variant sites on the same chromosome.” The hope is that “it is always more informative if you can link two markers together in the inheritance pattern (of a complex disease) than just use one marker or the other.” This project should be of great use in disease-gene findings, in pharmacogenetics, and in evolutionary studies.

The complete genome sequence (2,160,837 bases) of *Streptococcus pneumoniae* (a bacterium that causes a serious form of pneumonia) contains 2,236 predicted genes, and 64% were assigned a probable biological role [*Science* 2001; **293**: 410, 498]. Some of the genes appear to have been acquired—by *horizontal gene transfer*—from other bacteria.

The various means of searching for genes (in a newly sequenced genome) are subject to errors. For example, using homology-based annotation in the *Drosophila melanogaster* (fruit fly) genome [*Nature Genet* 2001; **27**: 337] yields an additional 1,042 new candidate genes.

An example was reported [*N Engl J Med* 2001; **344**: 539] in which sequencing the *BRCA1* gene found no mutation, in a patient with breast cancer. Examination of the patient’s germline DNA revealed that *BRCA1* transcription was “silenced” as the result of abnormal methylation in the gene’s 5'-flanking region. This is an example of an *epigenetic* cause of cancer.

A lot of reports have appeared on the effect of dioxin (TCDD; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin) on male rat sex organ development. Now comes a report that TCDD can affect female rats’ behavior [*Environ Health Perspect* 2001; **109**: 621].

Aug 2001 Will heresy never cease? A study has appeared [*Science* 2001; **293**: 1058, 1139] that

provides strong evidence that translation (of mRNA into protein)—usually agreed upon that it occurs in the cytoplasm of a cell—can also take place in the nucleus!

Previous issues of *Interface* have described the phenomenon of “RNA interference” (RNAi) whereby particular genes can be silenced (another form of *epigenetic* control). The RNA-induced silencing complex (RISC) contains short (~22 nt) RNAs derived from a double-stranded RNA trigger. Now the RNAi effector nuclease, *Argonaute2*, has been identified in nematode, fungus and mustard plant [*Science* 2001; **293**: 1146], bridging the gap between different phyla and helping prove that RNAi is, evolutionarily, a very old process.

Previous issues of *Interface* have described companies that wish to study isolated populations (e.g. Iceland) as a means of identifying genes involved with complex diseases, and we’ve described criticism of this approach [*Nature Genet* 2000; **22**: 139] predicting that linkage disequilibrium (LD) will not extend beyond 3 kb and that isolated populations will not provide any benefit unless there has been a very narrow *genetic bottleneck*, or the SNP in question is <0.05 frequency. Now comes an argument that the usefulness of isolated populations in dissecting complex traits should not be dismissed [*Nature Genet* 2001; **28**: 309]. First, the LD claim does not hold for SNPs relatively far from one another. Second, one can increase significantly the genotypic relative risk (GRR) and hence the ability to identify genes in isolation populations.

An analysis comparing the Celera and Ensembl predicted-gene sets [*Cell* 2001; **106**: 413] revealed that the novel genes predicted by both groups are largely non-overlapping!

Sep 2001 The Clinton administration during its final week set the upper limit for arsenic levels in water at 10 parts per billion (ppb), down from the previous 50 ppb. This upper limit was restored at 50 ppb last March [*Nature* 2001; **410**: 503] by the Environmental Protection Agency (EPA) who found insufficient evidence for altering this. Now, the U.S. National Academy of Sciences has reported that the cancer risk is 10-15 times greater than the EPA considers acceptable—even at arsenic levels below 10 ppb [*Nature* 2001; **413**: 341].

Bardet-Biedl syndrome (BBS) is a genetically heterogeneous disorder characterized by eye disease (*retinal dystrophy*), extra fingers or toes (*polydactyly*), obesity, delays in development, and kidney defects. Evidence is reported [*Science* 2001; **293**: 2213, 2256] that BBS might be a complex trait

requiring three mutant alleles (from at least two different genes) to become manifest; the authors suggest that this *tri-allelic* model of disease transmission might be a relatively simple model, compared with other much more complex (*multifactorial*) disorders—such as diabetes, hypertension, congestive heart disease, or dementia.

The original estimates of the total number of human genes (32,000 to 40,000 that we reported in *Interface* issue #20) are now shown [*Genomics* 2001; **77**: 71] to be higher—41,000 to 45,000—and other geneticists are predicting that the final total number may exceed 50,000 or 60,000.

Oct 2001 Studying a 3-generation family suffering from the “inability to speak,” Svante Pääbo of the Max Planck Institute (Leipzig, Germany) localized a “speaking” gene to a segment of chromosome 7. When Jane Hurst (Oxford) found a 5-year-old with a similar defect, who had a segment of chromosome 7 moved to another chromosome, they identified the *FOXP2* gene because it was located within the chromosomal break [*Science* 2001; **294**: 32]. *FOXP2* is a transcription factor containing a polyglutamine tract, a zinc-finger motif, and a forkhead DNA-binding domain. Now Pääbo is comparing this gene in nonhuman primates, to see if there might be a consistent difference between nonspeaking apes and humans who are able to speak.

A new society dedicated to promoting the discovery and free publication of information on the variations in human genes was inaugurated at the American Society of Human Genetics annual meeting in San Diego. It will be known as the Human Genome Variation Society (HGVS).

The Lasker Awards this year went to those who developed *embryonic stem-cell* research successfully and how to make *knockout mouse lines*: Mario Capecchi (Utah), Martin Evans (Cardiff University in England), and Oliver Smithies (Chapel Hill, North Carolina).

The generation of almost 700,000 open-reading-frame-expressed sequence tags (ORESTES, which provides sequence data from the protein-coding portion of transcripts) was shown [*Proc Natl Acad Sci USA* 2001; **98**: 12103] to significantly exceed the capacity of conventional expressed sequence tags (ESTs).

In the “RNA-interference world,” the total number of RNAi genes—conserved between plants, worms, flies and vertebrates—now looks like it may be in the hundreds, or even thousands, per each genome [*Science* 2001; **294**: 797, 853, 858, 862; *Cell* 2001; **107**: 823]!

The total genome of the bacterium that causes plague—*Yersinia pestis*—comprises a chromosome of 4.65 million bases (Mb) and three circular DNA plasmid molecules of 96, 70, and 9.6 kb. The complete sequence [*Nature* 2001; **413**: 467, 523] shows 21 regions displaying characteristics of pathogenicity and adaptation, probably acquired through *horizontal gene transfer*.

Nov 2001 A single gene, *Gp9*, encodes a *pheromone*-binding protein that appears to be crucial for fire ants to recognize one another (by smell) if they are from the same colony [*Science* 2001; **294**: 1434].

A “longevity gene,” *Prop1* in dwarf mice, combined with caloric restriction, extends the life span from less than 800 days to more than 1200 days, on average [*Nature* 2001; **414**: 412]. The Prophet of Pit-1 (*PROPI*) gene encodes a paired-class homeodomain transcription factor that is exclusively expressed in the developing mammalian pituitary gland. *PROPI* function is essential for anterior pituitary organogenesis, and heritable mutations in the gene are associated with combined pituitary hormone deficiency in human patients and animals.

The complete genome sequence of *Methanosarcina mazei*, a methane-generating archaeobacterium, has about 3300 predicted genes [*Science* 2001; **294**: 1634], about 1100 of which appear to have been captured by *horizontal gene transfer*! “The genome of *M.mazei* looks more like that of rhizobium bacteria (that fix nitrogen for plants) than that of other purple nonsulfur archaeobacteria.”

The genome of the microsporidian *Encephalitozoon cuniculi*, a parasite in many animals including humans, has only 2.9 million bases [*Nature* 2001; **414**: 401, 450]—even smaller than that of many bacteria. This parasite has chosen to lose most of its energy-metabolism genes and has cobbled together a fascinating alternative novel system for energy.

Patil and coworkers [*Science* 2001; **294**: 1669, 1719] have drawn up a haplotype map for the entire unique (nonrepetitive) DNA of human chromosome 21. *Haplotype* is the “pattern of co-occurrence of variant sites on the same chromosome.” Twenty different individuals, sequenced across ~21.7 Mb, and 19 more individuals sequenced across 2.7 Mb, revealed just three common haplotypes among 80% of their population. This is a far smaller haplotype number than previously thought.

A draft sequence of the puffer fish *Fugu rubripes* genome, just one-eighth the size of the human genome, has been completed by an international consortium in just one year [*Nature* 2001; **414**: 8].

Dec 2001 The complete sequence of human chromosome 20, nearly 60 Mb and the biggest of three chromosomes so far sequenced, is now reported [*Nature* 2001; **414**: 854, 863]. Chromosomes 22 and 21 had been previously sequenced.

Yet another soil microbe, *Agrobacterium tumefaciens*, has had its genome of 5.67 Mb sequenced [*Science* 2001; **294**: 2266, 2317, 2323]. The ability of this microbe to transfer DNA into plant cells has revolutionized plant and crop science, so scientists are searching for genes involved in “DNA transfer.”

DNA is transcribed to mRNA that is translated into protein. No diseases associated with translation defects had been found before now. Mutations in the **eIF2B** translation initiation factor gene have been shown to be responsible for a rare autosomal recessive neurological disorder, vanishing white matter [*Nature Genet* 2001; **29**: 358, 383].

The accuracy of a new computational approach to identify 5'-flanking regulatory regions and first exons has been described [*Nature Genet* 2001; **29**: **412**].

The Latest on the **BRCA2** Gene for Breast Cancer

Inheritance of one defective **BRCA2** allele predisposes a woman to breast cancer. Mice having no *Brca2* gene show substantial prenatal or perinatal lethality, and animals that do survive to adulthood develop lymphomas of the thymus. Therefore, Jonkers et al. [*Nature Genet* 2001; **29**: 418] generated a mouse line having an inducible *Brca2*(-/-) knockout plus deletion of the *Trp53* tumor suppressor gene (which is frequently mutated in **BRCA2**-associated cancers). Their results show that inactivation of the *Brca2* and *Trp53* genes combine to mediate breast cancers—indicating that disruption of the p53 pathway appears to be pivotal in **BRCA2**-associated breast cancer.

“Q” quote of the Month.....

Never go to a doctor whose office plants have died.....

Erma Bombeck (1927-1996)

The Human Genome, One Year Later

A great summary of the first year of unexpected findings, after announcing that “the human genome had been sequenced,” appeared in [*Genome Res* 2001; **11**: 645]. [1] Only 1-2% of the genome encodes protein. [2] A large number of duplicated genes, and portions of genes (even single exons!), exist nearby the gene of origin. [3] An unexpected number of genes appear to have been “captured” by *horizontal gene transfer* from other organisms. [4] More than half of the >98% noncoding portion represents interspersed repetitive DNA (reflecting remnants of transposons), and the remaining half is not “junk DNA” but should provide valuable insight into genome evolution. [5] Some regions contain >90% repetitive sequence in intervals of >500 kb, whereas other regions (e.g. the **HOX** gene clusters) are nearly completely devoid (<2%) of DNA repeats. [6] The function of ~5% of the genome, recognized as containing α -satellite sequences, is now widely thought to be associated with centromere function and telomere structure. [7] Important to our studies involving *gene-environment interactions*, it now appears that human *common* variant sites ($q \geq 0.10$) and *polymorphic* variant sites ($q \geq 0.01$)—when diverse world-wide populations are studied—will approach 6 million and 11 million, respectively. [8] The patterns of *recombination frequency* vary dramatically across the genome. [9] Single-nucleotide polymorphisms (SNPs; nucleotide substitutions) are most commonly seen in GC base-pairs (mutating to AT). [10] The best approach to sequencing a genome is the combination of the shotgun approach and focused sequencing.

Currently, more than one-third (>1 Gb) of the human genome is finished to an accuracy of <1 error per 10,000 bases, with the goal of finishing the other two-thirds during the next 2 years. Where are the most exciting areas left to go with the **Human Genome Project**? These areas include: studying evolution of the genome and genetic architecture; understanding how (what we used to call) “junk DNA” actually functions in chromosome structure, meiosis and mitosis, and gene expression; discovering ethnic differences in haplotype/allelic frequencies; and screening human variation and how it relates to complex diseases.

CEG Members in the News

Thomas Doetschman made invited presentations to the following: HHMI Excel Program for High School Students "Genetics and the Study of Heredity" (June 2001), the European Commission's QoL Integrated Projects in Functional Genomics (Nov 2001) and to the Graduate Studies Visitation Day on Mouse Genetic Engineering (Nov 2001).

Sohaib Khan was selected to be on the Board of Trustees of the Ohio Cancer Research Associates Inc., Columbus OH, in the fall of 2001, and a member of the editorial board of the journal "STEROIDS".

George Leikauf an invited lecture entitled "Strategic Transgenesis" was delivered at the Eighth International Inhalation Symposium, Hanover Medical School, Hanover, Germany (June 2001), and another invited lecture on "Acute lung injury: Functional genomics and genetic susceptibility" was delivered at the Thomas Petty Aspen Lung Conference, Aspen, CO (June, 2001).

Dan Nebert was an invited speaker in a symposium on "Transcription Factors and Cancer" at the 9th International Union of Toxicology (IUTOX) Congress of Toxicology (July 2001, Brisbane, Australia); an invited speaker at the 18th International Symposium on Polycyclic Aromatic Compounds (Sept 2001, Cincinnati, Ohio); gave the Plenary Lecture on "The Human Genome Project and the future of pharmacogenomics" at the Annual Meeting of the Joint Chinese-Australian Colleges of Pathologists (Oct 2001, Hong Kong); and chaired the session and introduced the topic "The Environmental Genome Project," Symposium on Gene Expression and Proteomics in Environmental Health Research," sponsored by the National Center for Toxicogenomics (NCT) and the National Institute of Environmental Health Sciences (NIEHS) (Dec 2001, Bethesda, Maryland).

Susan Pinney presented a poster entitled "Cancer incidence in a population living near a nuclear materials processing plant at Fernald, Ohio," at the Congress of Epidemiology, Toronto, Ontario, Canada (June 2001).

Alvaro Puga gave an invited talk on "Role of the aryl hydrocarbon receptor in cell cycle regulation" at the 9th International Union of Toxicology Congress in Brisbane, Australia, July 2001, and has been selected as a permanent member of the AITx-1 Study Section.

Peter Stambrook organized and chaired the workshop on Genomics, Proteomics and Bioinformatics: Environmental Mutagen Society, held in San Diego, CA (do you know when this was?). He was an invited Speaker at the 1st International Conference on Mechanisms of Action of Neutraceuticals in Dubrovnik, Croatia (Oct 2001). He is a member of the Board of Trustees of the American Cancer Society, Ohio Division, the FASEB Board of Directors, Committee to Evaluate Division of Extramural Research and Training (DETR) at the NIEHS, and the FASEB Public Affairs Executive Committee.

Glenn Talaska was a member of the Scientific and Organizing Committees for the 18th International Symposium, International Society for Polycyclic Aromatic Hydrocarbons, Cincinnati, OH (Sept 2001). He was also on the Scientific Committee for the 5th International Symposium on Biological Monitoring in Occupational and Environmental Health, Banff, Alberta, Canada (Sept 2001).

Yolanda Sanchez has been named one of the 20 most promising biomedical researchers in America by The Pew Charitable Trusts. Sanchez has received \$240,000 from the Trusts to help support her research over a four-year period. The Pew Scholar Awards are granted to researchers and investigators that show outstanding promise in the basic and clinical sciences, and are intended to encourage scholarly innovation. The awards provide flexible support to scholars as they establish their laboratories and continue their research in areas from AIDS to cancer, and from childhood infectious diseases to diseases affecting the elderly. Sanchez received the award for her research in understanding how cells respond to DNA damage. "This area of research may lead to better cancer treatment in the future," said Jerry Lingrel, PhD, professor and director of the Department of Molecular Genetics, Biochemistry and Microbiology. Sanchez is the third UC re-

CEG Members in the News (cont...)

searcher to receive a Pew Scholars Award during the last decade (June 2002).

David Warshawsky organized the 18th ISPAC meeting that was held at the University of Cincinnati, Sept 2001, and is on the editorial board of *Toxicological Sciences* (2001-2002). He is also the co-chair of the oversight committee for the University mass Spectrometry Facility.

Timothy Weaver received the Merit Award from NHLBI in 2001.

Jeff Whitset received the prestigious 2001 Daniel Drake Award - The University of Cincinnati.

June 4 Enquirer, 2001 Gene research growing at University of Cincinnati

By Tim Bonfield
The Cincinnati Enquirer

Tucked away in an unremarkable room in an out-of-the-way building at the University of Cincinnati, a team of three casually dressed researchers works in what looks like any other graduate-student science lab. But this isn't any other science lab. This 20-by-20-foot room, jammed with hundreds of thousands of dollars worth of equipment and computers, is UC's Genomics and Microarray Laboratory, one of the few "core" facilities in Greater Cincinnati playing a crucial role in boosting biomedical research. The lab is part of a broader effort at UC that already involves hundreds of scientists, hundreds of millions of dollars in grants and infinite possibilities for advancements in genetic research. Yet some say the work here needs to double in scale, to keep Cincinnati on pace with the exploding research opportunities flowing from the Human Genome Project, the massive national research effort that made history last year by defining all 3.1 billion base pairs of DNA making up the human genetic code. Cincinnati could become one of the 10 to 12 major centers for biomedical research nationwide, said Dr. Donald Harrison, senior vice president and provost for health affairs at the UC Medical Center. "This is the growth industry of the future, for the next two decades, for the entire

country," he said. "Every medical center in the country is trying to expand in these areas." The hope is that expanding genetic research will lead to important medical discoveries, which will inspire companies to form and create a variety of jobs as discoveries move from laboratory concepts to commercial products. UC hopes to double its biomedical research funding to about \$286 million a year by 2006, while adding hundreds of researchers and support staff, Dr. Harrison said. But a large part of this biomedical economic development vision depends on the work going on in the third-floor lab of the Kettering building, home of UC's department of environmental health. The lab, though a little cramped, is packed with powerful equipment. The hardware was purchased in November 1999, said **Puga**, director of the microarray lab. After several months of testing and troubleshooting, the lab started producing real genetic reports in February.

"The space is what we have," **Puga** said. "It looks small, but a lot is going on." In the back, tucked under a hanging shelf, rests a \$25,000 DNA amplifier, which creates samples of genetic material. There, two \$80,000 robots process the samples and prepare microwell racks, which can contain the equivalent of up to 384 test tubes. In the corner, under a glass box, is a \$65,000 microarrayer, which takes a mere 12 hours to "print" up to 10,000 genes at a time onto a single glass microscope slide. Just two years ago, it would take experts days to perform such work on just one gene. On a shelf above a large-screen computer terminal rests a featureless blue plastic box, about the size of a cable TV descrambler. This \$50,000 chunk of hardware contains a dual set of lasers that scan all those genes so they can appear on the computer as a grid of multicolored dots. And those dots — each no bigger than 100 microns across (about 1/250th of an inch) — are everything. They show which genes get turned on, and which ones get turned off, when a sample of healthy tissue is exposed to a disease-causing virus, bacteria or toxin. The dots also show how diseased tissue responds to a medication under development. Once the data are scanned, the microarray lab staff burns a CD of the data and

CEG Members in the News (cont...)

ships it off to the researcher who needs it. As scientists gain understanding of the complex genetic circuitry revealed by the dots, entire realms of treatment options emerge, **Puga** said. This is the kind of work that has allowed researchers nationwide to discover genes linked to many kinds of disease, from breast cancer to Alzheimer's. This is the technology that helped develop the breakthrough leukemia drug, Gleevec, recently approved by the FDA for wide-scale use. The newer, faster technology and completed gene maps mean the work is coming faster every year, said **Nebert**, professor of environmental genetics at UC. Research speed will leap yet again this summer, when a \$2.3 million supercomputer gets in stalled at Children's Hospital, **Nebert** said. That computer will allow faster interpretation of data from the microarray lab. In the 1980s, the average post-doctoral candidate in a university lab could isolate and analyze about 18 genetic base pairs a week, he said. This summer, they'll be able to do 1 million base pairs a week. Researchers are using UC's microarray lab to delve into the causes and possible treatments of cystic fibrosis and asthma, better treatments for head and neck cancers, analyses of rare types of hemophilia, genetic links to lung cancer, and a new understanding of how people may be affected by mixes of toxins found in Superfund environmental clean-up sites. **Nebert** envisions a day when people could have their genetic code scanned like a bar code, so doctors could detect health problems long before serious symptoms appear. Such data could also help doctors know exactly which drugs may best treat health problems and which ones could cause harmful side effects. None of this would be possible without the advances in computers and robotic technology at work in the Kettering building, **Nebert** said. Yet, as powerful as that equipment may be, it has limitations. "These machines speed up work, but they cannot replace good, sound science," he said. "You still have to interpret the results. You still have to have vision to develop solutions."

CENTER FOR ENVIRONMENTAL GENETICS WORKSHOP BIOINFORMATICS FACILITIES AND SERVICES CORE WORKSHOP

This workshop surveyed the opinions of CEG members regarding the role of the Bioinformatics F&S Core in relationship to their particular research needs. The feedback received during the workshop is being used to help prioritizing among possible services to be offered to center members by the core.

The workshop was opened by introductory comments from CEG Director, Marshall Anderson. Bruce Aronow, leader of the Bioinformatics Core, followed with a brief presentation about the general goals of the university-wide Bioinformatics initiative and how to tie the Center's Bioinformatics core in this process. Mario Medvedovic, a core member, described some of the services that the core offers regarding microarray data analysis. View the presentation online at:

<http://homepages.uc.edu/~medvedm/documents/CEG-Bioinformatics-12-7-01-C.pdf>

?????? If one can't
drink and drive,
why do bars have
parking lots ??????

Biotechnology, ...

What follows is a synopsis of some of the more interesting things that have happened during the last 6 months of 2001, with regard to genetically modified (GM) plants, biotechnology, and related topics, provided chronologically:

Jul 2001 Creating tea and coffee plants that are genetically deficient in caffeine synthase (and therefore have no caffeine) is an important advance for people who might want the benefits of tea without the unwanted side effect of a rapid pulse [*Nature* 2000; **406**: 956].

The problem using numerous “immortalized” cell culture lines in the same laboratory room is that one cell line can contaminate another. The most notorious “contaminant” is the cervical carcinoma line HeLa, named after the 31-year-old donor **Henrietta Lacks**. HeLa cells are incredibly healthy and divide rapidly in culture. Now, techniques are being developed—based on the same principles as those used in forensic medicine—to confirm that one cell line is contaminated with another. This involves using short tandem repeats (STRs), which are unique to any individual and therefore to any human cell line [*Proc Natl Acad Sci USA* 2001; **98**: 7656].

Aug 2001 Two independent studies were recently published on herbicide use of the Roundup Ready (RR) soybean, the first large-scale GM crop to hit the market in 1996. The two reports drew conflicting conclusions. One (from Idaho) states that RR soybeans “clearly require more herbicides than conventional soybeans” and claims that the yield of RR soybeans can be as much as 10% less than the yield of conventional soybeans. The other report (from The Netherlands) indicates that RR soybean use across the U.S. “has led to a moderate reduction in herbicide use” [*Nature Biotechnol* 2001; **19**: 700].

A great boon to farmers, especially cotton growers, has been the use over the past 5 years of crops having the GM insecticide, *Bacillus thuringiensis* (Bt). Now comes word that insects can adapt to Bt, just as they do to any chemical pesticide! The actual mechanism of developing resistance by the tobacco budworm was shown to involve the gene encoding β -1,3-galactosyl-transferase, which adds carbohydrates to lipids and proteins. Such carbohydrate addition to the Bt protein receptor is needed for its toxicity. The resistant

budworm lost this enzyme and therefore became resistant to Bt [*Science* 2001; **293**: 778, 857].

Over the past several years, great concern has been expressed about manure-based environmental pollution, especially in areas growing a lot of pigs. Now comes the “phytase transgenic pig” [*Nature Biotechnol* 2001; **19**: 741]. The saliva of these pigs contains the enzyme phytase, which allows them to digest the phosphorus in phytate—the most abundant source of phosphorus in the pig’s diet. This reduces fecal phosphate by as much as 75% and leads to a more environmentally-friendly pig!

Sep 2001 How do U.S. human geneticists view Celera’s commercialization of the Human Genome Project? Among the most-cited advantages are [a] that Celera is forcing the federal government-sponsored HGP to move more quickly, and [b] enormous amounts of new sequence data are becoming available very rapidly. Among the most-cited disadvantages are [a] companies are staking claims on pieces of DNA with a barrage of patents, [b] commercial companies are profiting on the federal data being available, and [c] this erodes international agreements not to patent raw DNA data [*Nature Genet* 2001; **29**: 15].

Oct 2001 The impact of Bt-toxin expressing corn pollen on monarch butterfly populations, and the problem of insects now becoming resistant to Bt, are further summarized in a Commentary [*Proc Natl Acad Sci USA* 2001; **98**: 12328]. Moreover, the government of India has ordered the burning of illegal GM cotton [*Science* 2001; **294**: 991].

A big surprise in the field of biotechnology [*Nature* 2001; **414**:135] came when Incyte Genomics (San Diego) announced on 24 Oct 01 that it would stop making DNA chips—after being one of the leaders in that emerging technology.

Certain organic tins are used to paint the hulls of ships so that algae and mollusks cannot attach (actually slowing down the ship’s speed). On 5 Oct 02, representatives of the 159 member states of the International Maritime Organization signed an agreement to ban these *organotins*. Tributyl tin, especially, is known to cause apoptosis (programmed cell death) and can impair the immune system [*Environ Health Perspect* 2001; **109**: A579].

Nov 2001 As discussed in earlier issues of *Interface*, Myriad Genetics (Salt Lake City) has a patent that covers “all methods for diagnosing a

predisposition for breast and ovarian cancer associated with the *BRCA1* gene.” The Institut Curie (Paris) has begun an opposition procedure with the European Patent Office (EPO) in München, saying that the patent is too broad and—sequencing the gene (meaning only all introns and exons)—“fails to detect 10-20% of all expected mutations” [*Nature Biotechnol* 2001; **19**: 1004].

The latest article on Science and Society [*Trends Genet* 2001; **17**: 670] further claims that the effect of gene patents is “to monopolize and therefore to retard, rather than stimulate, both scientific and economic progress.”

Amidst so many reports in the popular and scientific press about genetic, immunological, aging, and other developmental problems in cloned animals, Lanza et al. [*Science* 2001; **294**: 1893] evaluated 24 sexually mature cattle that had been cloned by usual somatic-cell procedures and found all of these cows to be healthy and normal.

In a mound of documents left in Kabul when the Taliban fled the city 12 Nov 01 [*Science* 2001; **294**: 1823], was a top-secret atomic bomb recipe: “fashion plutonium into giant orbs using rubber cement, surround them with a mix of dynamite and Play-Dough, and add a remote-control mechanism from a toy car.” This is literally a joke—part of an article from a 1979 issue of the *Journal of Irreproducible Results*, a mock journal based in Boston that lampoons real science!

Dec 2001 Most transgenic work involves female cells such as oocytes, fertilized eggs and blastocysts. Sperm stem cells appear to be impossible to culture and frequently will “silence” the *trans*-gene. A new technique from Brinster’s lab (Philadelphia) has created the first transgenic mice from genetically-modified *sperm* stem cells [*Proc Natl Acad Sci USA* 2001; **98**: 13090].

Ethical, Legal and Social Issues, ...

What follows is a synopsis of some of the more interesting things that have happened during the last 6 months of 2001 with ethical, legal and social issues (ELSI) related to the Human Genome Project, provided chronologically:

Jul 2001 After controlling for personal income, education and occupation, Watson and coworkers found that living in a disadvantaged neighborhood is associated with an increased incidence of coronary heart disease [*N Engl J Med* 2001; 345: 99, 134]. This form of inequity has been termed “environmental justice.”

In recent years the research community and the public have been engaged in a re-examination of the ethics and responsible conduct of research involving human subjects. “We must accept that in all such research, ethics and science are not separable. Every study must conform to ethical standards or it should not be performed, and it must be scientifically sound or it cannot be ethical” [*N Engl J Med* 2001; **345**: 136].

A report stemming from the February 2001 United Nations Environmental Protection (UNEP) Governing Council meeting in Nairobi describes the threats to indigenous cultures from globalization. It is estimated that “up to 90% of the world’s 5,000 to 7,000 spoken languages could die out over the next century, and with them a valuable storehouse of information about the natural world” [*Environ Health Perspect* 2001; **109**: A307].

Sep 2001 A report earlier in the year [April issue of *Nature Genet* 2001] has created a stir about racial differences in the handling of drugs. More than ten dozen commonly prescribed drugs are metabolized, at least in part, by the cytochromes P450, CYP3A4 and CYP3A5. In the U.S. it was found that ~60% of African Americans and only 25-30% of Caucasians have the active CYP3A5 enzyme [*Environ Health Perspect* 2001; **109**: A418]. This suggests that—given the recommended dose of a drug—African Americans might be at least two times more likely to have

adverse effects from an overdose.

Creating a map of islands of human linkage disequilibrium “is the next logical step for the Human Genome Project” [*Nature Biotechnol* 2001; **19**: 795]. There is debate about trying to construct haplotype maps for Africans, East Asians, Caucasians, Pacific Islanders, and Amerindians. Those opposed suggest that this “might have made sense 1,000 years ago,” but today—with centuries of increased travel and therefore so much interbreeding between races—the problem of a large amount of *genetic admixture* makes this unrealistic.

Seldin’s lab at UC Davis suggests that ethnic-difference markers (EDMs) can help in distinguishing individuals, however; looking at more than 600 markers in large numbers of African Americans versus Mexican Americans, they found 151 EDMs that could be readily identified [*Am J Hum Genet* 2001; **70**: 737]. This suggests that more accurate and robust genetic clusters—identified by genotyping a modest number of neutral markers—can be inferred without having any knowledge of ethnicity or the color of the patient’s skin [*Nature Genet* 2001; **29**: 247, 265]. This “race-neutral approach” is also the subject of an editorial [*Nature Genet* 2001; **29**: 239].

Nov 2001 The British government has suspended the use of genetic testing results to determine premiums for life insurance [*Nature* 2001; **414**: 6]. The 5-year moratorium is an attempt to halt the trend of insurers using data from such tests to set policy rates.

LETTERS TO THE EDITOR

RESPONSES/COMMENTS TO VARIOUS QUESTIONS

Q In the last issue you described how Gleevec (also called STI-571) works as a super pill for curing certain types of cancer. Now, I hear that the drug has some serious problems?

A *In one study, 53 of 54 patients suffering from the early phase of chronic myeloid leukemia (CML) showed complete lasting success [*N Engl J Med* 201; **344**: 1031]. Patients suffering from the later phase of CML called the “blast crisis” responded well at first, but most have now relapsed with a few months despite continued treatment. The cause of this relapse has already been identified [*Science* 2001; **293**: 876]. The CML malignant cells are able to develop mutations in Gleevec’s target protein (known as p210 BCR-ABL), thereby making the chemotherapeutic agent no longer effective in blocking growth. Again, it just goes to show you: cancer cells are just like bacteria, or insects, or probably all organisms on this planet, as far as being able to develop resistance against something they don’t like. This is **Evolution** in the true sense. We are witnessing evolution before our very eyes...!!*

COMMENT Concerning “the largest known number,” I think this number should be associated with something that the human mind can comprehend. I propose that the largest number be that of the number of electrons that can comfortably fit within the 3-dimensional space of the known boundaries of our universe.

A *Good idea. But here is another story of the “how many angels can dance on the head of a pin?” Computer hobbyists have just discovered the largest prime number ever—which has 4 million digits [*Science* 2001; **294**: 2087]. The new prime number is $2^{13,466,917} - 1$, which surpasses the previously known largest prime number of $2^{6,972,593} - 1$. Meanwhile, the search continues for bigger and bigger prime numbers yet.*

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**If what you want
lies buried, dig
until you find**

.....*anonymous.*