Issue Number 6

INTERFACE:
GENES AND THE ENVIRONMENT

CENTER FOR ENVIRONMENTAL GENETICS UNIVERSITY OF CINCINNATI Autumn 1995

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# The Environment, Genes, and Asthma

Perhaps one of the most pressing needs in the study of environmental health science is to understand better the etiology (causes) of asthma. Arguably, asthma is one of the most important environmental diseases that clearly has an underlying "genetic predisposition" (*i.e.* a tendency for some persons, but not others, to get the disease). Millions of people have asthma. Possibly due to the high prevalence of a disease characterized by large variations in severity, asthma is commonly misunderstood. It is often thought of as only a "mild disorder." Or a "disease of children," who start to wheeze because of their pet cat. Also, too much emphasis is erroneously placed on the psychosomatic aspects of this disease.

***The Harsh Reality***

More than 12 million Americans will tell you that their asthma is a ***complex disease***. Asthma is usually not associated with any identifiable allergen (substance causing an allergy) and, interestingly, this disease is often acquired during adulthood. Alarmingly, the incidence of hospital admissions and deaths due to asthma has risen over the last 15 to 20 years—at a time when pharmacologic therapy and intervention for this disease has improved. Asthma is more prevalent in urban settings and, with more urbanization, severe asthma will probably remain a concern into the 21st century.

The dilemma that surrounds the asthma epidemic has led to several scientific approaches to understand risk factors associated with this disease. Over the last decade, the role of airway epithelial injury and the mediators of inflammation (***cytokines*** and ***eicosanoids***) have become better understood. This increased understanding has altered strategies for long-term control. These strategies include bronchodilators (containing compounds that mimic neurotransmitters) and anti-inflammatory drugs (such as corticosteroids), which have improved the quality of life for the unfortunate person with asthma. Emphasis today has been placed on aggressive, early intervention, which heads off and reverses mucosal inflammation, rather than on an over-reliance on bronchodilators alone, which relieve smooth muscle contraction.

***Every little breeze whispers a wheeze***

**Concerns about outdoor air.** Air quality standards are designed to protect "susceptible individuals" in the population, and susceptible individuals surely include persons with asthma—those who have additional risk from the adverse effects of air pollution. Past inhalation studies have demonstrated that ***"bronchoconstrictive substances"*** (things that close down the airways and block breathing) affect breathing in asthmatic subjects at lower concentrations than that in healthy subjects. Bronchoconstrictive substances include compounds such as sulfur dioxide and nitrogen oxides. Likewise, other air pollutants (*e.g.* ozone) lower the threshold of the effects of bronchoconstrictive antigens (which stimulate antibody production). High ambient ozone levels are associated with increased hospital admissions and emergency room visits for asthma. Other epidemiological studies find an association between the amounts of ***particulate matter*** (*e.g.* soot) and the prevalence of either asthmatic symptoms (wheeze, cough, and chest tightness) or decreased lung function (ability to exhale). Studies conducted throughout the world find that both allergic (atopic) and non-atopic individuals with asthma are affected by particulate matter. Environmental pollutants having the strongest association with respiratory disease are "fine particles" (possessing a median diameter of less than 2.5 micrometers).

**Concerns about indoor air.** Because only about 10 percent of our time is spent outdoors, the quality of indoor air is of great concern. This is especially true, since persons with asthma may stay inside to avoid air pollution. Environmental tobacco smoke, particularly when mom lights up around the kids, has been associated with asthma. This effect may be related to the role of tobacco smoke in contributing to the fine particulate matter inside the home or to the tobacco smoke's effect of increasing respiratory tract infections. One estimate is that environmental tobacco smoke leads to more than 140,000 hospital admissions per year among exposed children.

***Outdoor ozone*** is lower in concentration inside buildings than outside, due to indoor chemical "sinks" (substances which absorb) for ozone. In contrast, ***outdoor particulate matter*** in the fine-size range can easily penetrate

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into the indoor environment. The levels of fine particulate matter indoors are often as much as 85% of that found outdoors. Indoor allergens—including house dust mite, cockroach material, cat dander and fungal spores—can also precipitate or exacerbate (make worse) asthma. So, there is no place like home to attack asthma—or, to have an asthmatic attack!

**Occupational medicine and asthma.** Other clues about environmental chemicals that appear to induce or affect asthma have come from occupational medicine studies. For example, isocyanate-based paints are often used to produce the shiny surface finish on automobiles. Historically, 5% to 10% of all ***polyisocyanate*** workers are known to develop occupational asthma! Other compounds that can cause asthma include aldehydes, acid anhydrides and certain metals. Although these compounds may sound rare to you, more than 6,000 facilities throughout the United States release greater than 55 million pounds of substances known to cause asthma into the ambient air (according to the 1990 U.S. Environmental Protection Agency emission inventory). This estimate excludes several hundreds of millions of pounds of chlorine, styrene, volatile organic compounds, and other irritants that are also known to exacerbate asthma.

***The "Asthma Gene"***

With the explosion in molecular biology and genetics, coupled with recent advances in the Human Genome Project (HGP), more and more "disease genes" are being discovered. Nonetheless, caution is recommended when it comes to asthma. The next time you see a newspaper report about a research team claiming to have found ***the*** asthma gene, be sure to read the report carefully!

Human geneticists are challenged and stretched to their limits by diseases such as asthma, which most likely is a complex collection of symptoms governed by multiple genes *[multiple genes contributing to a single-disease trait, i.e. "**multiplex phenotypes**," were discussed in issue #4 of this NewsLetter]*. **Twin studies.** Homozygotic (identical) twins are a useful starting place. Being born with the same DNA, twins with asthma should be able to help us discern the "role of nature" (genetics) from the "role of nurture" (environment). The term "identical twins" seems pristine, until you examine the actual medical histories of twin pairs and asthma. My colleagues and I enjoyed a trip last summer to the "Twins' Festival" in Twinsburg, Ohio. When more than 1500 twin pairs congregate, a good time will certainly ensue! We observed the excited claims about who are the most identical, and the least identical, twin pairs.

Along with Drs. Jonathan Bernstein and Maureen Miller of the Department of Immunology, we have begun to investigate risk factors and the genetic basis of asthma. Our initial data—with 20 ***concordant*** (*i.e.* both have asthma) and 16 ***discordant*** (*i.e.* one, but not the other, has asthma) twin pairs—indicate that childhood exposure to environmental tobacco smoke is highly correlated with asthmatic "disease severity scores" in adults. This suggests that early environmental exposures can increase the "penetrance" of the disease trait (phenotype). Because this is an ongoing study, we may have more findings to report in a future issue of ***Interface***.

Historically, other investigators have examined the incidence of asthma among twin pairs. Scientifically, there is some good news and some bad news. First, the bad news for environmental geneticists (or, is it good news?) is that, if your twin has asthma, your odds of developing this disease are only 1 in 6 (my goodness, wouldn't one have predicted at least a 50:50 chance, or odds of 1 in 2?). This suggests that, even though you carry the gene(s) for getting asthma, environmental exposure is needed to bring out the disease (again, we're talking about "low penetrance"). Indeed, the necessity of environmental exposure seems to be a key factor in the etiology of asthma.

**Splitting the phenotype.** So, where else should we look? Since asthma is complex and can be caused by a wide array of agents, let's subdivide the disease into different obvious "classes." This is called "splitting the phenotype." Since we know that some asthmatic patients also exhibit ***atopy*** (*i.e.* hypersensitivity of the skin, eye or upper respiratory tract in response to identifiable agents, or ***allergens***), let's see if these two features are genetically linked. One objective measure of atopy is serum immunoglobulin E (IgE) levels. IgE levels are high in certain families and, in general, are higher in persons with atopic asthma. In other words, persons with allergic asthma almost always have high IgE in their serum, so, perhaps these two traits are linked. Therefore, would the "allergy gene" be near the "asthma gene" on the same chromosome? In fact, a scientific gold rush is on; many colleagues would like to lay claim to a piece of DNA, or gene (or ***locus***), that regulates IgE expression. Candidate chromosomes include number 11 and number 5 [actually, 11q and 5q, for those who are minding their p's (short arms) and q's (long arms) of chromosomes]. Which proteins (gene products) will be associated with each locus and how these might be associated with atopy, as well as with asthma, is up in the air at this time.

**Receptors and cytokines.** Another approach by scientists is to use what is known about proteins important to the disease, and "work backwards" to the DNA. Candidates here include the variable region of the immunoglobulin receptor (called the ***V-beta subunit***) found on the lymphocyte, a white blood cell (more specifically, a ***T-cell***, because it originates in the **t**hymus) which is very important in the role of immunity. The variable region will be altered, from one T-cell clone to another, depending on the acquisition of immunity; this could, in turn, reflect one's capacity to adapt to adversity. Other candidate proteins include the ***cytokines***, particularly the interleukins (IL's) that are released by activated T-cells, as well as other cells during inflammation. Emphasis here has been placed on the interleukin important to directing cell traffic, or ***chemokines***, such as IL-8 and related molecules. Other scientists are hunting for cytokines, such as IL-4 and IL-5, that are important in cell maturation and that play key roles in the eosinophil—a cell often found in the inflamed airway of asthmatic patients.

Back to splitting our phenotype. Ultimately, asthma is a disease in which a wide array of environmental stimuli can cause a wide array of mediators to be released, which, in turn, activates a wide array of cell types. Confused yet? Now you see what scientists in this area are up against when trying to get a handle on the genetics of asthma.

So, why not just look at airway muscle and what contracts it? Little muscles in the airways contract, or relax, when a specialized protein on the cell surface (called a receptor) sees its ***neurotransmitter***. The airways contract in response to ***acetylcholine***, and relax in response to ***epinephrine*** (adrenaline). (Have you ever wondered why a needle full of epinephrine is taped to the walls of emergency rooms? It's there for an emergency, in order to dilate the airways of a person in acute bronchospasm, which was possibly induced by an allergic reaction to a drug or foreign substance.)

To explore the receptor site that binds neurotransmitter molecules, scientists can use a process called ***site-specific mutagenesis***. Here, the functional consequences of directed mutations for a ***subtype of the adrenergic receptors*** are being characterized by a research team led by Dr. Steve Liggett, a new member of the CEG. They found that certain mutations (leading to changes in one or more amino acids) cause diminished function (bronchial relaxation), whereas other mutations have no effect at all. Interestingly, these errors were then found to occur in nature (*i.e.* in certain humans), and to be more frequent in individuals having a certain type of asthma. This type of asthma, often called ***nocturnal asthma***, comes on at night, is refractory to bronchodilator therapy, and is more frequently associated with particular mutations in the adrenergic receptor. So, the gene for the adrenergic receptor appears to be "one of the asthma genes" we're looking for. Again, while exciting, these results are preliminary, and genetic testing has only been done on a few dozen patients. How many "asthma genes" might there be? It is not unreasonable to think that there might be 20 or more. Nonetheless, small advances are being made into a genetic basis for controlling asthma.

***The Harsh Reality Remains...***

In the final analysis, then, asthma is a disease in which a wide array of environmental stimuli can cause a wide array of intercellular mediators to be released; these, in turn, activate a wide array of cell types. It therefore comes as no surprise that asthma represents a multiplex phenotype, and we predict that it will take at least several more years to sort out, completely, the genetics of this disease. **—Contributed by George D. Leikauf**

# CEG Members in the News

**Carol Rice** has been appointed to the External Advisory Board of the Y-12 Beryllium Worker Enhanced Medical Surveillance Program at Oak Ridge, Tennessee. The project is designed to evaluate the utility of the lymphocyte proliferation test for the detection of beryllium sensitization.

Glenn Talaska has been invited to speak at a Molecular Epidemiology Workshop, jointly sponsored by the Italian and United States National Cancer Institutes (Portofino, Italy) November, 1995. The talk will be entitled ***"Noninvasive methods to detect DNA adducts in target tissues in relation to occupational exposures."***

**Alvaro Puga** will speak on ***"The role of Y-box transcription factors in the oxidative stress response"*** at the 2nd Annual Xenobiotic Metabolism and Toxicity Workshop of Balkan Countries (Ioannina, Greece) October, 1995.

**Dave Warshawsky** gave a talk entitled ***"The assessment of carcinogens in vitro"*** and **Eula Bingham** discussed ***"Regulatory considerations for cell culture applications"*** at the Society for In Vitro Biology Meeting (Cincinnati, Ohio) October, 1995.

**Jack Loper** and **Wilson Tabor** are coordinating a Superfund-supported basic research program to develop an environmental education outreach program, which promotes interactive education and action-based programs within the Ohio River watershed region. The goal of this program is to increase the public's understanding of issues relating to public health and the environment in a technological society, and will foster a more positive attitude towards the role the scientific community might play in dealing with these problems. The program will give people access to knowledge that will allow them to make clear choices between what they see as necessary versus what can be done on the basis of competing priorities. This collaboration will involve local school districts and regional environmental education groups -- including the Rivers Unlimited Mill Creek Restoration Project, the educational and public affairs division of the Fernald Environmental Restoration Management Corporation (FERMCO), and the Ohio River Basin Consortium for Research and Education.

**Dan Nebert** has been invited to speak at a one-day symposium on ***"Genetic Susceptibility to Environmental Disease"*** and panel discussion the next day at the 49th NIEHS Center Director's Meeting in November, 1995. Speakers include Jack Taylor (NIEHS; target gene damage), Arno Motulsky (Seattle; vascular disease), Ken Korach (NIEHS; estrogen receptors), Dan Nebert (Cincinnati; genetics of metabolism), Roger Wiseman (NIEHS; breast and ovarian cancer), Jack Taylor, Doug Bell and Cary Weinberger (all from NIEHS) will join in the panel discussion. This meeting, one of a series that meets approximately ever six months, will be held in Chapel Hill, North Carolina.

**Joanna Groden** is part of a team of researchers who have cloned the (***BLM***) gene for Bloom's Syndrome, an inherited type of dwarfism. All Bloom's Syndrome patients eventually develop cancer, and the identification and characterization of this gene could help scientists learn more about why cancer forms in healthy patients. The findings were published in the November 17th issue of the journal ***Cell.***

# Government Performance and Results Act (GPRA) of 1993

The GPRA states that Congress will require strategic plans from virtually all federal agencies by Autumn of 1997. Furthermore, Congress wants "performance plans" that link the strategic plans with specific "output" and "outcome" measures -- as well as "annual performance reports" which would indicate how well agencies are "meeting their goals." The most unsettling problem, for the National Institutes of Health (NIH) and the National Science Foundation (NSF), however, is that the GPRA and basic research are fundamentally incompatible. There is no association between "outcomes of basic research" and "predictable goals." Likely outcomes of basic research cannot be quantified.

Let me get this straight. A law now exists that obviously does not apply to basic research. Those who wrote the law, and those monitoring its compliance, acknowledge that the law probably cannot pertain to basic research. Yet, heads of federal agencies funding basic research are being asked to comply with the law. As Alice in Wonderland exclaimed, "Things are getting curiouser and curiouser."

## Why should governments be worried about their budget deficits?

The furlough of U.S. government employees in November and again in December occurred because of differences in opinion about how to deal with the annual budget deficit. France is also having her troubles with budget deficits and the total national debt. How concerned should we be?

The concern has to do with ***globalization***. Presently, international-currency markets are so large and efficient that funds quickly find their way to where they can be invested safely and profitably -- explaining why the Deutschemark and the Yen are doing so well. "Real interest rates" in the U.S. are higher than they have been (ca. 4% a year) -- a measure of the cost of funding the budget deficit, as well as a sign that the market people expect "something will go wrong."

For federally funded science, there appears to be painful times ahead. The only secure prospects of growth are in the costs of (a) funding new debt and (b) paying interest on what has already accumulated. Responsible governments are those smart enough to read the signals.

## Plants Make Haze While the Sun Shines

A recent report in ***Nature*** addresses the phenomenon of the bluish haze hanging over wooded hills such as Virginia's Blue Ridge Mountains. In the 1960's, botanist F.W. Went determined that hydrocarbon gases given off by trees were responsible. Why do the plants go to the trouble of producing it? Researchers surmise that they main haze component, isoprene, is used as a strategy for coping with heat.

Chris Geron, who does atmospheric modeling for the Environmental Protection Agency (Research Triangle Park, North Carolina) is investigating the role that plants play in ozone formation and the overall effects these emissions have on air quality. The levels of isoprene in the atmosphere are higher (three to five times) than previously thought. These plant hydrocarbons are being produced through a mighty effort but without an apparent function. Isoprene alone siphons off 2% of the carbon fixed through photosynthesis that could be converted to sugars. Why would these plants waste so much energy?

Isoprene is known to evaporate quickly, which would cause the plant to produce more as the temperature rises. Researchers have found that this thermal protection mechanism is used in plant species that are subject to short burst of high temperature (as one might experience in the Appalachian Mountains) -- as opposed to desert plants which use a more efficient way to cope with constant heat.

Methanol is another culprit, which is less reactive but emits levels comparable to isoprene. Efforts to identify and measure this compound and other unknown ingredients of plant haze are underway. The fact that these natural sources of hydrocarbons have outweighed any human contributions has led regulatory agencies to rethink their ozone strategies, especially in rural and heavily wooded areas.

# LETTERS TO THE EDITOR

### RESPONSES TO VARIOUS QUESTIONS

**Q** **Reduced glutathione (GSH) is, alas, a SOFT NUCLEOPHILE, not a "soft electrophile," as I had written in Issue #5. Is this correction worth reporting in an Erratum in the next issue?**

**—Howard G. Shertzer**

**A** *Consider your correction a done deal!*
*—Daniel W. Nebert*

**COMMENT:** **Back in issue #1 we described a possible association between the "Gulf War Syndrome" and the human paraoxonase (*PON*) polymorphism. In issue #2 it was noted that soldiers were given pyridostigmine, an antidote of anticholinesterase poisoning, and that variations in the response to pyridostigmine are likely to reflect allelic differences in the *PON* gene.**

**According to Professor Mohamed Abou-Donia at Duke University, the combined (synergistic) effects from three chemicals used by U.S. soldiers during the Persian Gulf War might have caused some of the symptoms reported (chronic fatigue, rashes, headaches, weight loss and joint pain). These chemicals are pyridostigmine, *N,N*-diethyl-*m*-toluamide (DEET), and permethrin. At the outset of the conflict, soldiers were given a 21-count package of 30-mg pyridostigmine anti-nerve gas pills; fear of chemical warfare "might have prompted many soldiers to take more than the recommended dosage of pyridostigmine pills." DEET, an insect repellant, was used at 90% concentrations, due to concern about insect-borne tropical illnesses. Soldiers' uniforms were impregnated with the insecticide permethrin, as well as with DEET. The combination of dermal exposures to permethrin and DEET, and high doses of oral pyridostigmine, might have led to a delayed toxic impact known as "organophosphate-induced delayed neurotoxicity" (OPIDN).**

**While Abou-Donia's recent research and speculations might shed light on the connection between environmental exposures and some medical symptoms associated with what is unofficially referred to as the Gulf War Syndrome, it still does not explain why some individuals appear to be more sensitive than others to the chemical effects [*Environ Health Perspect* 103: 793 (1995)]. Perhaps the human *PON* polymorphism is an additional factor in the synergistic effects of three or more chemicals.**

**Another point about the Gulf War Syndrome is that never, in the history of warfare, have so many U.S. soldiers survived and so few died during combat! Thus, morbidity (from viral and bacterial infections, insect bites, exposure to chemicals, etc.) became a much greater concern than normal — [*The Persian Gulf Experience and Health*, NIH Technology Assessment Workshop Statement (April 27-29, 1994)].**

**Q** **In issue #3 you explain that defects in the *BRCA1* gene lead to "an 82% lifetime risk of breast cancer," as well as increased risk of ovarian and prostate cancer. But, how common is the defective gene? And, what is the normal function of the *BRCA1* gene?**

**A** *These are very timely questions. The latest estimate is that the 185delAG mutation in the **BRCA1** gene accounts for 16% of breast cancer and 39% of ovarian cancer—diagnosed before age 50 in Ashkenazi Jewish women [**Nature Genetics 11:** 113-4, 1995]. These studies also suggest that about 1 in 100 Ashkenazi Jewish women carry the **BRCA1** frameshift mutation, in stark contrast to the estimated 1 in 833 carrier frequency of all **BRCA1** mutations in the general Caucasian population. Obviously, this report has aroused a lot of interest, and already many women are going to their physicians and asking to be tested to see if they are genetically susceptible. It is quite likely that the carrier frequencies in Asian and Black populations will be reported soon.*

*The "normal function of the human **BRCA1** gene" is being investigated as we speak. The mouse **Brca1** gene was recently found to be expressed in rapidly proliferating cell types during differentiation. In the mouse mammary gland, **Brca1** expression is enhanced during puberty, pregnancy, and following treatment of ovariectomized animals with estradiol and progesterone. These data suggest that the BRCA1 protein is important during the processes of cell division and differentiation in multiple tissues, notably in the mammary gland in response to ovarian hormones [**Nature Genetics 11:** 17-26, 1995].*

# Observations by a Biologist

## Travel eastward is worse than travel westward

As most of us scientists know, traveling quickly across several time zones can wipe you our for the meeting you will attend, or the seminar that you are planning to give the next day -- a constellation of symptoms known as ***"jet lag."*** Now, L.D. Recht, R.A . Lew and J. Schwartz (University of Massachusetts Medical School) have tried to quantitate this phenomenon, by measuring games lost by a traveling baseball team [***Nature* 377**:583, 1995]. Studying the 1991-93 complete season records of the 19 North American major league baseball teams based in cities of the Eastern and Pacific time zones, Recht and coworkers concentrated on the two games immediately before and after each time zone passed). Statistical analysis showed that the home team could expect to score 1.24 more runs than usual when the visitor has just completed eastward travel (***P*** = 0.006), but not after the visitor has just completed westward travel!

This story just confirms the commonly observed difficulty of the first day of meetings when Americans travel to Europe, compared with that when Europeans travel to North America!

# SCIENCE LITE

## The Slovakian Fellow and the Czech Fellow

Once there were two Czechoslovakian Postdoctoral Fellows working with me and Susan in the laboratory of Professor Walter Schmidtlapp. Then, that country broke up geographically. So, instead we had a Slovakian Postdoctoral Fellow and a Czechian Postdoctoral Fellow in our laboratory. Recently, both the Slovak and the Czech mysteriously disappeared, along with the can containing our lab's coffee funds. Rumor had it that $27.19 was missing.

Trying hard to make ends meet in these days of increasing financial difficulties throughout the scientific community (but especially in our laboratory), Professor Schmidtlapp insisted that we lay aside our pipettes and track down these thieves. Before the trail had grown cold, Susan and I were soon tracking the Slovakian and the Czechian Postdoctoral Fellows northward through Canada! In Toronto and Edmonton, and again in the Yukon Territory, each time that we telephoned our mentor Professor Schmidtlapp, he would say, "Just as soon as you find these scoundrels and get that money back, write me a check and send it through the mail!" Susan and I agreed and pressed on.

Just beyond Fairbanks, Alaska, we had heard that the two postdoctoral fellows were camping in the wilderness and, on a snowmobile, approached their reported location with caution. To our shock and utter dismay, their campsite was a mess, and two polar bears -- one male and one female -- were still milling around, looking very suspicious. There was blood and torn clothing on the snow. With great emotion, I attacked the nearest bear with a hand machete and , sure enough, inside the female polar bear I found the poor Slovak's chewed up body. While I was attaching the other bear, the mobile telephone in the nearby pup tent was ringing. Susan answered it, exclaiming loudly, "Professor Schmidtlapp wants to know where the $27.19 is!" About that same time I had opened the stomach of the second bear and confirmed what I had painfully suspected. I shouted back to Susan, "Tell Dr. Schmidtlapp that **the Czech is in the male!**"

# RECENT CEG-SPONSORED SPEAKERS

**OCTOBER 11, 1995**
**Henry Weiner, PhD**
Professor of Biochemistry
Purdue University
West Lafayette, Indiana
**"Liver mitochondria aldehyde dehydrogenase: studies on catalysis, import and processing"**

**OCTOBER 17, 1995 (Distinguished Lecturer)**
**OCTOBER 17, 1995 (Departmental Seminar)**
**Werner Kalow, MD**
Professor Emeritus
Department of Pharmacology
University of Toronto
Toronto, Ontarion M5S 1A8, Canada
**"Evolutionary processes from a pharmacogenetist's perspective"**
**"A new polymorphism affecting S-oxazpam glucuronidation"**

# Diet Causes Viral Mutation in Mice

Recent reports indicate that a benign coxsackie virus can become virulent, if its host lacks selenium in its diet. The work of Charles J. Gauntt (University of Texas Health and Science Center, San Antonio) and Steven Tracy (University of Nebraska Medical Center, Omaha) is the first to show that a ***nutritional deficiency*** can cause a virus to evolve from benign to virulent in an intact animal.

Because most viruses are benign, of the 20 million people who are infected annually in the United States, only about 10,000 exhibit symptoms of illness -- ranging from colds to inflammation of the lining around the heart (pericarditis).

Melinda Beck (University of North Carolina) and other researchers have linked coxsackie virus and heart disease to selenium intake in humans as well as mice. People deficient in the mineral tend to develope ***Keshan disease***, an inflammatory heart disease. These patients were also found to have the virus. Beck and her colleagues reported that a normally benign strain of coxsackie virus damaged the hears of selenium-deficient mice. Injecting the virus from these animals into selenium-rich mice caused the heart disease in health mice.

The researchers speculate that the virus changes rapidly in a selenium-deficient host, because the animal's immune system is lacking in the protective mechanisms which selenium (an antioxidant) provides. Coxsackie viruses mutate readily, but it is now known how many mutations must occur before the virus becomes virulent.

The fact that these viruses become virulent, when they infect nutritionally-deprived people, may provide insight as to why there is a prevalence of new strains of influenza virus in selenium-deficient areas of China. These findings may also explain how the HIV virus can cross over to a new host species, such as what might have occurred when infected monkeys passed the HIV virus to humans living in selenium-poor areas of Africa.

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