

Sanity remains defined simply by the ability to cope with insane conditions.

Ana Castillo

*Massacre of the Dreamers (1994)*

HEARING

# PCBs Alter Brain Development

Exposure to the non-coplanar polychlorinated biphenyl PCB95 during gestation and nursing causes abnormal development of the auditory cortex in rats, affecting the brain's representation of what is heard, according to new research in the 1 May 2007 issue of *Proceedings of the National Academy of Sciences*. Since children with autism and other developmental disorders show abnormal responses to sound, suspicions have been raised that PCB95 and similar molecules in the environment might promote this problem and perhaps other language/cognition disorders in children.

Prior to their being banned in the late 1970s as potential carcinogens, PCBs became ubiquitous environmental pollutants that continue to threaten human health. Their molecular stability has maintained them intact, and they have entered the food chain, accumulating in the fat of exposed organisms.

Most of the early work on PCB-associated health problems focused on the coplanar molecules, but there is now evidence that non-coplanar PCBs may cause

trouble of their own (coplanar and non-coplanar refer to the chemical structure of the PCBs in question). "They are reported to prevent dopamine production in monkey brains, to alter behavior in rats, and may even alter neuropsychological functioning in children," explains first author Tal Kenet, a faculty member at Harvard Medical School and Massachusetts General Hospital. "Our research suggests they cause abnormalities in the development of the auditory part of the rat brain."

The researchers fed pregnant rats 6 mg/kg of PCB95 in corn oil daily from day 5 of pregnancy until the weaning of their pups. "We then mapped the boundary and response characteristics of the primary auditory cortex of the pups using a series of electrodes implanted in the brain," says Kenet. "Individual neurons were monitored to see which characteristic sound frequency they responded to." The auditory cortex is one of the first sensory systems to mature.

The maps of the PCB95-exposed rats were found to be oddly shaped and had "holes" in them where neurons seemed not to respond to sound. The maps also included many neurons that showed a lack of frequency selectivity, and the typical posterior-to-anterior distribution of neurons responding to ever higher frequencies was disorganized.

"This must affect how their brains interpret sound," says Kenet. "In addition, we recorded notable imbalances in inhibitory and excitatory signaling between the auditory cortex nerve cells. Without proper balancing, the correct representation of sound cannot be guaranteed. Importantly, children with autism show evidence of imbalances between excitation and inhibition in the brain, but whether it's the same type of imbalance remains to be explored."

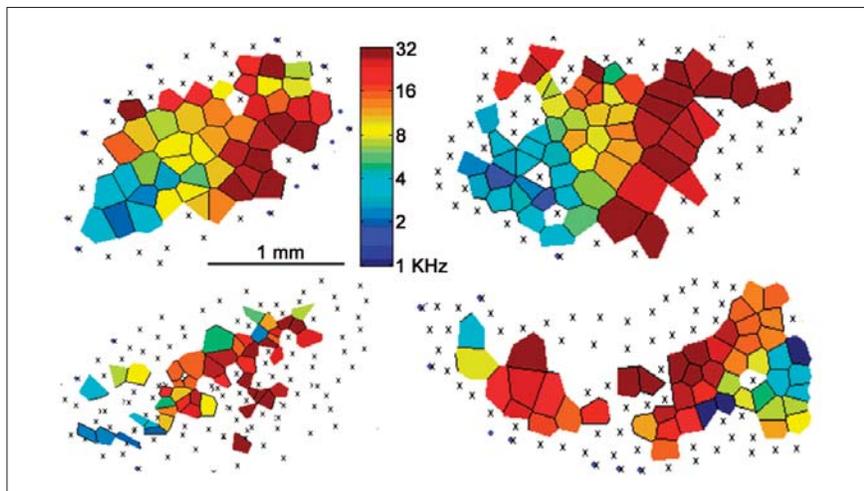
The researchers also found the plasticity of the PCB-exposed cortices to be abnormal. Usually, if rat pups are exposed to a particular tone, the area of the cortex that deals with that frequency expands. "That did not happen in the PCB-exposed pups," says Kenet.

"Epidemiological studies have found that children with prenatal PCB exposure do more poorly on tests of verbal learning and memory," says Susan Schantz, a professor of veterinary biosciences at the University of Illinois at Urbana-Champaign College of Veterinary Medicine. "These exciting new findings suggest that underlying changes in the development or plasticity of the auditory cortex may be responsible for those effects." However, Schantz cautions that the rats in these studies received a very high dose of a very potent PCB congener. "In my opinion," she says, "it is unlikely that human infants, even those living in highly polluted areas, would be exposed to similar concentrations. We also need to keep in mind that any effects observed in humans are likely to be much more subtle than the striking changes observed in these rats."

"It would be interesting to know whether animals closer to humans develop disorders resembling autism or other cognitive problems after [environmentally relevant] PCB95 exposures," remarks Jesús Pastor, a senior researcher at the Centre for Environmental Sciences in Madrid, Spain. "That might help reveal how serious this problem could be."

Since PCBs can be passed on to human infants in breast milk, the report raises the question of whether some mothers in highly polluted areas—perhaps those whose family history points toward a possible genetic risk of autism spectrum disorders—should bottle-feed rather than breastfeed. However, "some research shows that breastfeeding may actually lessen the negative impact of prenatal exposure, even though children who are breastfed have higher overall body burdens of PCBs," says Schantz.

—Adrian Burton



Top left shows a tonotopic map of the primary auditory cortex of a normal rat pup. At the left end of the map are neurons that are selective for low-frequency tones (blues); at the other end are neurons that respond only to high-frequency tones (reds). This pattern is usually smooth (i.e., no holes), continuous (gradually changing from one end to the other), and elliptical in shape. The other three examples above are from rats exposed to PCB95. These maps are neither continuous nor smooth, are very disorganized, and have erratic shapes.

Source: Kenet T et al. 2007. Perinatal exposure to a noncoplanar polychlorinated biphenyl alters tonotopy, receptive fields, and plasticity in rat primary auditory cortex. *Proc Natl Acad Sci USA* 104(18):7646-7651.

## NEUROLOGY

## Dementia and Secondhand Smoke

Secondhand smoke is known to be associated with cardiovascular disease, which in turn is a known risk factor for dementia, but little research has examined the latter end point with regard to secondhand smoke. Research presented at the 28 April–5 May 2007 annual meeting of the American Academy of Neurology now suggests that increased risk of Alzheimer disease and other forms of dementia may well belong on the long list of potential health effects from chronic exposure to secondhand smoke.



“When we started this study, . . . we knew of the likely pathway through cardiovascular disease, but we were also interested in an independent pathway from secondhand smoke [directly] to dementia,” says principal investigator Thaddeus Haight, a senior statistician at the University of California, Berkeley. That direct pathway did not bear out, but the team did make a new discovery regarding the cardiovascular link.

Haight and his colleagues analyzed health data for elders with and without cardiovascular disease that had been collected through the Cardiovascular Health Study, a national study of cardiovascular disease risk factors in adults older than 65. Of the 3,602 participants who had been evaluated for dementia, 985 had no history of cardiovascular disease or symptoms of dementia and had never smoked, and 495 reported an average of nearly 28 years of secondhand smoke exposure.

The group most highly exposed to secondhand smoke—those with a lifetime exposure of more than 30 years—had a 30% greater risk for developing dementia compared with the no-exposure group. Within the highly exposed group, people with subclinical cardiovascular disease (defined as narrowing of the carotid artery) had an even higher risk, nearly 2.5 times that of the no-exposure group. “There weren’t really any independent effects due to secondhand smoke exposure alone, but there were effects through a pathway other than clinical cardiovascular disease,” says Haight. “In people with indications of subclinical disease, . . . the greater the exposure to secondhand smoke, the more elevated the risk of dementia.”

“These results are definitely not surprising; they are completely in line with what we know about heart health and brain health—that both are extremely interconnected,” says Maria Carrillo, director of medical and scientific relations for the Alzheimer’s Association national office. “Anything that makes it more difficult for your heart to pump blood through your body will ultimately affect how your body pumps blood into the brain. That compromised brain blood volume really makes a difference after years of exposure.”

Haight and his colleagues are currently working to confirm their findings. He says, “What would be interesting from this work that we’ve done so far is to extend it to look at the risk of dementia in those with a history of secondhand smoke exposure who have diabetes or hypertension.”

—Julia R. Barrett

## Indian Subcontinent Gets Environmental Monitoring

Members of an Indo-U.S. workshop report in the 13 April 2007 issue of *Science* that to understand and slow global environmental change, there needs to be a global network of environmental data collection. Currently, much of Africa and the Indian subcontinent lacks such a network, although these areas have considerable influence on the regional and global environment. To help alleviate this information shortage, the Indian government is developing a new monitoring network known as INDOFLUX. This network will generate the needed baseline data from which to evaluate future environmental changes in a country where much of the population depends on natural resources and coastal integrity.

## Manufacturing Energy Use: Room for Improvement

The U.S. EPA has released a report that outlines energy use trends in 12 manufacturing sectors representing about 85% of total industrial energy use in the country. *Energy Trends in Selected Manufacturing Sectors* shows that industry has significant opportunities for improving its environmental performance through adopting energy-efficient and clean-energy technologies. The report also projects that with a “business-as-usual” scenario, total energy consumption of the sectors studied could increase by 20% over 2004 levels in the next 13 years, and that CO<sub>2</sub> emissions could increase by 14%. The EPA further determined that use of renewable fuels in industry is now higher than in the residential, commercial, and transportation sectors, and is growing.

## California Rules on Formaldehyde

Citing studies on throat cancer, workplace asthma, and increased asthma and allergies in children, the California Air Resources Board has adopted new restrictions on formaldehyde that will cut by nearly 60% the amount of the chemical emitted into air from the resins and glues used to bond plywood, particleboard, and medium-density fiberboard. The total amount of formaldehyde emitted into California’s air each year will be reduced from the current 650 tons to 150 tons. The new rule will be phased in beginning in 2009, with full implementation in 2012. It will apply to all products sold, used, or made for sale in the state. Manufacturers will need to obtain third-party certification, maintain records, and label all wood or wood products to show compliance with the law.

## GINA Passes in House

The Genetic Information Nondiscrimination Act (GINA), first introduced in the House 12 years ago, was finally approved by that chamber in April 2007. GINA prohibits the wrongful use of genetic information in the making of hiring and health insurance decisions. Genetic factors are linked to 15% of all cancers and 10% of adult chronic diseases such as heart disease and diabetes. More than 200 organizations from different sectors have endorsed GINA, which had bipartisan support in the House with more than 200 cosponsors. The bill now goes to the Senate, which has passed it twice in recent years. President Bush has already voiced his support for the legislation.

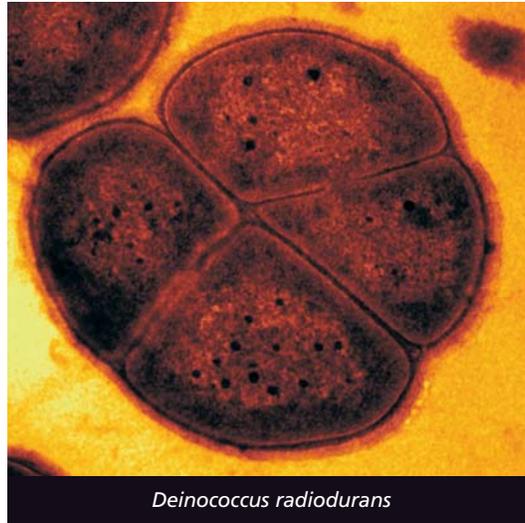
## MOLECULAR BIOLOGY

## What Is Radiation's True Target?

Radiobiologists have long believed that ionizing radiation, like gamma rays, kills cells by shattering DNA. Now Michael Daly, an associate professor of pathology at the Uniformed Services University of the Health Sciences, contends that proteins—not DNA—are the most sensitive targets, at least in some radiation-sensitive bacteria. Moreover, Daly's team discovered a novel manganese complex that appears to protect proteins from gamma rays. This new perspective comes from working with *Deinococcus radiodurans*, a bacterium nicknamed "Conan the Bacterium" because it survives huge radiation doses.

For 15 years, Daly probed DNA, genes, and chromosomal packaging for clues to how *Deinococcus* defies death. He noticed that *Deinococcus* and other radiation-resistant bacteria accumulated high levels of manganese, compared with radiation-sensitive bacteria. When zapped with the same dose of gamma rays, however, radiation-resistant and radiation-sensitive bacteria all experienced about the same number of double-strand DNA breaks. Daly reported these results in the 5 November 2004 *Science*, then tackled the remaining question: What does manganese protect in radiation-resistant bacteria?

The latest proof-of-concept experiments, published in the April 2007 *PLoS Biology*, showed that manganese neutralized reactive oxygen species (ROS),



*Deinococcus radiodurans*

or free radicals, generated by ionizing radiation. When the researchers bombarded radiation-resistant bacteria with gamma rays, manganese appeared to protect proteins from a form of oxidative damage called carbonylation. But in radiation-sensitive bacteria with little manganese, gamma rays caused high levels of protein oxidation, and the microbes died. Shifting the emphasis from DNA to proteins "is heretical," Daly admits, "but the data speak for themselves."

Daly's surprising results "fly in the face of fifty years of dogma," says John Battista, a professor of microbiology at Louisiana State University. Gamma rays cause a variety of DNA lesions, and Daly measured only double-strand breaks, one of the least abundant types. "I would be more convinced if he measured a more abundant lesion like thymine glycol levels," says Battista.

Daly's laboratory has most recently identified a small manganese complex in *Deinococcus* that is extremely resistant to ionizing radiation and protects proteins but not DNA. Daly plans to pursue practical applications for the manganese complex in mammalian cells, such as protecting people against radiation sickness, or sparing healthy cells from the ravages of radiation during cancer treatment. Many toxicants—including tobacco smoke, ultraviolet light, and heavy metals—damage cells via the production of ROS. If the complex prevents ROS damage to proteins in mammalian cells, too, other applications might someday include a lotion that could protect skin from ultraviolet rays. "All this lies ahead to be proven," Daly says. —Carol Potera

## DIET AND NUTRITION

## Sunny Side of Cancer Prevention

Many studies have linked higher latitudes with greater breast cancer risk, and seasonal variations are now thought to influence cancer incidence and mortality. The pivotal mediators in these relationships are believed to be sunshine and vitamin D. In clinical studies, poor vitamin D status is associated with a substantial increase in breast cancer incidence and mortality, though until recently, there has been only limited evidence in humans that vitamin D-related factors may reduce breast cancer risk. New studies are now clarifying the role of this nutrient.

For most people, sunshine is the main source of vitamin D and specifically of 25(OH)D. Vitamin D is unusual among nutrients because very few foods naturally contain it, and supplementation is intended primarily to compensate for a deficiency of sunshine. Most human photosynthesis occurs in the summer, because the angle of sunlight largely determines the rate of vitamin D synthesis. Among the better-defined mechanisms

of vitamin D's anticancer action are its ability to induce cell differentiation and apoptosis of cancer cells while also inhibiting cell proliferation, angiogenesis, and metastasis.

In the March 2007 issue of *Cancer Epidemiology Biomarkers & Prevention*, authors from Mount Sinai Hospital in Toronto described a case-control study involving 972 women with newly diagnosed invasive breast cancer and 1,135 healthy controls. All participants were interviewed to assess vitamin D-related exposures, such as outdoor activities, sun exposure habits (e.g., use of sunscreen), and dietary contributions (cod liver oil and milk consumption). More frequent sun exposure during adolescence was associated with a 35% reduction in breast cancer risk later in life. Lower risk was also linked to cod liver oil intake and drinking at least 10 glasses of milk per week. Milder protection was seen for people aged 20 to 29, but not for people over age 45.

"Our study suggests that vitamin D-related exposures during adolescence and early adulthood, when the breasts are developing, may be more important than later exposure," says lead author Julia Knight, a senior investigator at Toronto's Prosserman Centre for Health Research. "A study in postmenopausal

women asking about recent diet or sun would miss an effect of earlier exposure."

Knight is also interested in knowing what effect sunlight supplementation may have in women following treatment for breast cancer. An epidemiologic study of different regions of Norway, each with a different annual UV exposure, found that the prognosis was 15–25% better for women diagnosed (and thus treated) in the summer versus the winter. This research was published in the May 2007 issue of *Breast Cancer Research and Treatment*.

A second study out of Laval University in Quebec sought to assess seasonal variations of breast density, a biomarker of breast cancer risk. The goal was to compare such variation, if any, with blood levels of 25(OH)D. It was assumed that a delay or lag time might be likely between a change in 25(OH)D levels and the resulting change in breast density. The researchers recruited 741 premenopausal women at screening mammography and found a strong inverse correlation between mammographic breast density and circulating vitamin D levels. When a four-month lag time was assumed, seasonal variations of breast density and circulating vitamin D appeared to be highly

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## NARSAD: The Mental Health Research Association

In the early 1980s, three leading national mental health groups came together to form the American Schizophrenia Association. Since that time the organization has evolved in both name and scope; it is now known as NARSAD: The Mental Health Research Association to reflect its current focus on a wide range of mental disorders. NARSAD works not only to fund research to prevent, diagnose, and treat psychiatric diseases, but also to educate the public about these conditions. Visitors can find information on these initiatives and more at <http://www.narsad.org/>.

The Diseases and Conditions section of the NARSAD site is divided into six main sections: schizophrenia, depression, bipolar disorder, anxiety, childhood disorders, and other disorders. Each section offers a brief overview of the illness on which it focuses and a summary of symptoms and treatments. Insight into NARSAD's research into the illness is also available. In addition, feature stories on related topics are provided, as is information for people recently diagnosed with the illness, including resources for learning about the illness they have been diagnosed with and the medications they have been prescribed.

The Research Center portion of the NARSAD site provides information for potential grant recipients on how to apply for funding, provides a list of grantees, and notifies visitors of NARSAD grant deadlines. A section of project summaries gives visitors a look at the work NARSAD supports. Among other projects are a twin study to tease out the nongenetic family background contributions to depression and a mouse study of how changes in maternal behavior associated with a genetic modification may be passed to offspring that do not possess the modification. —Erin E. Dooley

synchronized, so much so that “variations of breast density appeared to be a mirror image of those of 25(OH)D,” the researchers wrote in the May 2007 issue of *Cancer Epidemiology Biomarkers & Prevention*.

“Taking seasonal variations and lag time into account appears to be crucial when studying the relation of circulating vitamin D to breast density,” says lead author Jacques Brisson, a professor in the Department of Social and Preventive Medicine at Laval University. “These time-related variables may also be crucial when studying the effect of vitamin D supplementation, because the latter is likely to vary with time, typically being more pronounced in fall and winter, for example.”

Brisson and Knight agree that the next step is to carry out randomized trials of the effect of vitamin D supplementation, as only this type of design would establish causality between high vitamin D intake and reduction in breast cancer risk. A randomized controlled study published in the June 2007 issue of the *American Journal of Clinical Nutrition* found that women who regularly took vitamin D<sub>3</sub> and calcium had a 60% reduction in all-cancer incidence compared with a group taking placebos and a 77%

reduction when the analysis was confined to cancers diagnosed after the first 12 months. Observational studies such as those spearheaded by Brisson and Knight have suggested a less dramatic reduction in cancer risk (50% or more).

Public health officials agree that limiting sun exposure will reduce the rate of skin cancers, but some scientists worry that such advice may lead to undesirable tradeoffs on a massive scale. “There are at most one or two extra skin cancer deaths [per hundred thousand people] when you compare the northern to southern United States . . . versus about thirty or forty fewer deaths for the other major cancers,” says Reinhold Vieth, an associate professor of nutrition at the University of Toronto. “So if you tally up the number of deaths likely to be attributable to UV light or vitamin D, it does not look like the most sensible policy to tell people to keep out of the sun just to prevent skin cancer.” Vieth's advice is for white people to expose more skin for a shorter time, for example by lying in a bathing suit for 10 minutes on each side, twice per week, and over 4 to 8 weeks of summer. Darker-skinned people should stay in the sun longer or take vitamin D supplements. —M. Nathaniel Mead



## 2007 Goldman Environmental Prize

On 23 April 2007, the 2007 Goldman Environmental Prize was awarded in San Francisco to grassroots activists from around the world to honor their work in protecting the environment of their communities. This year's winners are (above, clockwise from top left)

- Sophia Rabliauskas of Canada, who secured interim protection for the boreal forest of Manitoba against logging and hydropower development while the area's future is decided by the government and international agencies.
- Hammerskjöld Simwina of Zambia, who developed an innovative sustainable community development program that protects biodiversity and helps alleviate poverty.
- Tsetsegee Munkhbayar of Mongolia, who worked with government and grassroots organizations to halt unregulated mining operations that threatened the country's scarce water resources.
- Julio Cusurichi of Peru, who gained protection for an area of the remote Peruvian Amazon against logging and mining, preserving a sensitive ecosystem and the rights of indigenous peoples.
- Willie Corduff of Ireland, who headed a group of activists and landowners in successfully halting the construction of an illegally approved petroleum pipeline.
- Orri Vigfússon of Iceland, who negotiated an agreement with governments and corporations to end destructive commercial salmon fishing practices in the region.