The Tokyo Attacks in Retrospect
Sarin Leads to Memory Loss

In the wake of the 11 September 2001 terrorist attacks on New York City and Washington, D.C., the threat posed by chemical and biological weapons has instantaneously evolved from the theoretical nightmare to clear and present danger. Under this new set of circumstances, any addition to the body of scientific knowledge about the health effects of chemical or biological agents is particularly timely. In this month’s issue, a group of Japanese researchers led by Yuji Nishiwaki report the results of their investigation into the long-term physical and psychiatric effects of acute poisoning by sarin, a deadly military nerve gas [EHP 109:1169–1173].

On 20 March 1995, members of the Aum Shinrikyo religious cult released sarin in the Tokyo subway, using umbrellas to puncture newspaper-wrapped bags of the gas as they left the trains. Twelve people were killed in the incident, and more than 5,500 required emergency medical treatment. Although several studies have looked at the acute clinical manifestations of sarin poisoning, the authors felt there was an urgent need to perform an epidemiologic study of the chronic effects of sublethal exposures to sarin.

The team examined rescue workers and police officers who had been dispatched to the scene and were exposed to sarin in the course of performing their duties—a group of subjects with similar occupational, socioeconomic, and educational backgrounds. The study included 56 exposed subjects from the Tokyo fire and police departments, who were subdivided into high- and low-exposure groups, and 52 nonexposed subjects of similar backgrounds from the same departments. The research was conducted three years after the exposure.

To assess neurobehavioral effects, the investigators administered five tests designed to measure psychomotor function and memory function. A significant causal relationship was discovered between exposure to sarin and memory disturbance. The exposed group performed less well, in a dose–effect manner, than the control group in the digit span memory test. In this test, the subject is asked to memorize a series of digits displayed on a computer screen at 1-second intervals and then enter the digits into the computer in the correct order within 10 seconds. Later, the subject is asked to enter the digits in reverse order. It was this backward digit portion of the test that uncovered significant memory loss in the exposed subjects. Other tests suggested other exposure-related memory effects, but the results were not statistically significant.

Subjects were also given psychometric tests to assess traumatic stress symptoms, in order to examine whether there was any correlation between psychologic stress and chronic physiologic effects. No such correlation was discovered.

The authors conclude that their findings suggest causality between the sarin attack and memory disturbance, although the mechanism behind that disturbance is unclear. They recommend further study of the link between sarin exposure and memory loss.

--Ernie Hood

Bad News for Boys
Linking Hypospadias and Endocrine Disruptors

Hypospadias, or the arrested development of several parts of the penis, including the urethra, foreskin, and ventral surface, is usually not a topic for public discussion. But a review of research on the condition points to a link between hypospadias and endocrine-disrupting chemicals, one that Laurence Baskin of the University of California at San Francisco and colleagues are working to bring to the attention of the public and the public health community [EHP 109:1175–1183]. In their review article in this issue, the scientists conclude that the link between hypospadias, which occurs in 1 of every 125 live male births in the United States, and exposure to endocrine-disrupting environmental chemicals is a strong one, while environmental estrogens appear to not be involved. They also suggest that an antiandrogen mechanism may cause hypospadias.

Hypospadias can entail a displacement of the urethral opening to points along the shaft, within the scrotum, or even in the perineum. Severe cases result in penile curvature or ambiguous genitalia, making immediate and accurate sex assignment of the newborn difficult. Hypospadias is generally correctable by surgery, but complications from such procedures and psychosocial problems can result.

The condition has increased in prevalence over the past 14 years in the United States, nearly doubling between 1968 and 1993, according to the Centers for Disease Control and Prevention. The authors suggest this increase may be due to environmental chemicals encountered by pregnant women. However, very few of the 15,000 chemicals in the highest-volume production in the United States have been tested for endocrine-disrupting effects during development at any dose. Principal investigator Theo Colborn, who is director of the World Wildlife Fund’s Wildlife and Contaminants Program, cautions women who anticipate becoming pregnant or who learn they are pregnant to be exceptionally careful about their diet and environment, at least until they pass childbearing age. More and more, the evidence reveals that the embryonic and fetal stages of development are the most sensitive to endocrine disruption, she says.

Laboratory evidence strongly suggests that endocrine disruptors interfere with development of the male urogenital system, the team reports. So far,
the review shows, researchers have found no evidence that environmental estrogens or female hormones impede male urogenital development, despite their feminizing effects on males. Although not all mechanisms are known for some chemicals that cause hypospadias, in the current study the team found solid data pointing to an antian- drogen mechanism, one that hampers the activity of male hormones. But, says Colborn, “In light of the myriad chemicals in the environment today, demonstrating a causal relationship among humans will be difficult, time consuming, and costly.” Moreover, other causes are indicated, including genetic or chromosomal damage or defects and possibly other risk factors such as maternal age and low birth weight.

The authors credit not only increased basic research on urogenital development for providing clues to how certain chemicals might cause hypospadias, but also interdisciplinary research where developmental biology and toxicology converged and provided even more insight. These disciplines in turn relied on advances in molecular, cellular, biochemical, morphologic, and functional research for shedding new light on the relation between hypospadias and endocrine disruption—for revealing that an antiandrogen mechanism is involved while environmental estrogens are not. But the authors point out that much remains to be learned about normal development and about what causes hypospadias as well as many other health problems.

The team would like to see more directed basic research that focuses on developing screens and accompanying assays to test chemicals for their endocrine-disrupting effects (currently there are no standardized protocols to determine whether a chemical is a possible endocrine disruptor). But it will take more than a simple battery of tests using receptor binding to reduce exposure. ‘This lack of screens and assays is the rate-limiting factor that is slowing down the removal of endocrine disruptors from the environment,’ Colborn says. –Julie Wakefield

How Risky Is Rover?

Petting Transfers Pesticides

Although children can be exposed to pesticides through many means, including carpets, house dust, and chemically treated lawns and gardens, one important potential source is pets treated with parasite control products. According to the American Veterinary Medical Association, dogs are the most popular U.S. pets, with an estimated 53.6 million dogs owned as pets in the United States as of 1998. Those dogs could be a source of insecticide exposure to the millions of children who come into direct contact with them. Moreover, other pets and domestic animals treated for insect pests may be a large additional source of exposure.

Parasite control products often contain carbamate, pyrethroid, or organophosphate insecticides. To estimate the amount of transferable residues that children could obtain from their treated pets, J. Scott Boone and colleagues at Mississippi State University studied the organophosphate chlorpyrifos, used until recently in commercial dips used to treat dogs and cats for fleas and ticks [EHP 109:1109–1114].

The dark side of puppy love. Pet dips offer more than protection against fleas and ticks—they may also give unsuspecting pet owners an unhealthy dose of pesticide exposure.

The scientists found that young children could receive chlorpyrifos doses nearly equal to the U.S. Environmental Protection Agency (EPA) reference dose, or the amount a person can be exposed to daily without risk of adverse health effects over a lifetime. Although chlorpyrifos has since been withdrawn from the domestic use market, human exposure to other flea- and tick-control pesticides from pets and livestock could occur in much the same way.

Twelve dogs of similar breeds and weights were dipped with a nonprescription commercial flea dip, according to the manufacturer’s guidelines, for four consecutive treatments at three-week intervals, with no shampooing in between. Another 12 dogs were shampooed in between dips. Chlorpyrifos samples were taken from the dogs’ fur before and after dipping by rubbing the animals with cotton gloves.

Samples collected at 4 hours and at 7, 14, and 21 days after treatment from dogs that were not shampooed averaged 971, 157, 70, and 26 µg chlorpyrifos, respectively. Samples from dogs that were shampooed averaged 459, 49, 15, and 10 µg, respectively. Most of the transferable chlorpyrifos residues dissipated after 3 weeks, with the sharpest decrease after 1 week.

Humans are therefore at the greatest potential risk of exposure to chlorpyrifos shortly after treatment. Children, particularly, spend much time with pets and may be more sensitive to pesticide exposures than adults, so plausible estimates of exposure levels are needed to calculate risk. The researchers calculate that if a child plays with a dog for 5 minutes within 24 hours of the dip, petting and rubbing the dog over an 80-square-inch area, the child could be exposed to an average of 0.9–1.9 mg/kg chlorpyrifos. If the child weighs 25 kg (55 lb), the absorbed dosage could be 0.0011–0.0023 mg/kg. (The EPA’s reference dose for chlorpyrifos exposure is 0.003 mg/kg/day.) By contrast, in a 79.5 kg (175 lb) adult, the absorbed dosage could be 0.0003–0.0007 mg/kg.

Activities of butyrylcholinesterase (BChE) and acetylcholinesterase (AChE) were assayed in the dogs’ blood plasma as possible biomarkers of exposure to chlorpyrifos. These cholinesterases (ChEs) break down the neurotransmitter acetylcholine. This prevents overloading of the cholinergic system, which could result in effects ranging from headache to coma. Because humans and dogs have similar percentages of BChE and AChE in their plasma, the results may have implications for human health.

BChE was inhibited by 50–75% throughout the study; AChE was inhibited by 11–18% in dogs that were not shampooed, and to a lesser extent in dogs that were. Greater plasma ChE inhibition was observed at 7 days than at 4 hours, which might reflect the bioactivation of chlorpyrifos to chlorpyrifos-oxon (the active metabolite). Surprisingly, dog plasma ChE activity did not return to control levels during the 21-day period. Indeed, ChE activity inhibition in the blood was maintained at 60–80% throughout the experiment.

Currently, there is no perfect technique for measuring human exposure to flea- and tick-control pesticides from pets and livestock and assessing the attendant risk. Given the large number of pesticides in use, however, the cotton glove dosimeter model could be a quick, reliable, and useful tool for evaluating potential pesticide exposure. –Julian Josephson