other aspects of this terrible disease."

The ultimate goal, of course, is finding a cure for Huntington's. As Collins says: "That's the dream; that's what it's really all about." But finding the gene is not the same as finding the cure, and reaching that goal is certain to be every bit as eventful and frustrating as the HD gene search. Since the gene is completely unknown, researchers first have to determine what the protein produced by the normal HD gene does and how it's affected by the mutation. Presumably, Gusella says, it causes a "gain of function," whereby the gene is somehow given a new, erroneous task in the body. But finding out what that is won't be easy, given that the gene sequence provides no clues.

The researchers also want to know why the expanding, repetitious mutation affects the brain so severely, even though the gene is active in cells throughout the body. To answer such questions, Housman's group is now working on genetically engineering mice to contain the HD gene with its extra CAG repeats to see how it affects neuronal or other cell functions. "That's the high priority now," says Housman.

The researchers may have another long slog ahead of them as they look for the answers to their many questions. "We're starting with everything unknown," MacDonald says. "It's going to take some time." Researchers studying genes with expanded trinucleotide repeats in other diseases agree. "This is now the fourth disease involving this type of mutation, and I'm afraid it's a very thorny problem," says David Nelson of Baylor College of Medicine, one of the researchers who found that the defective gene in fragile-X syndrome, an inherited form of mental retardation, has extra copies of the triplet CGG. He points out that very little is known about the effects of such mutations, and the instability of the long repeats makes them technically difficult to work with.

Even though the next phase of research will be as arduous as the first, the consortium is nevertheless—and understandably—in a celebratory mood. The members are unsure if they will continue to stay together as a group. "No one has even talked about that yet," says Gusella, although he and others are sure they will all remain friends. In the meantime, the consortium plans a huge "blow out" party in May in Florida. And in Venezuela, home to a very large HD family, Wexler will have another at the Red Bull Bar, which is soon to be torn down to make way for a medical clinic and hospice for HD patients. "We're going to keep going, working and raising money to find a cure," she says. "If it turns out that our grandkids are saved because of the work we're doing, I'll be in seventh heaven."

–Virginia Morell

With reporting by Leslie Roberts.

MEETING BRIEFS

Toxicologists–and Snow–Descend on New Orleans

Neither rain nor snow nor sleet nor hail could keep 4000 toxicologists from descending on New Orleans last month (14–18 March) for the annual meeting of the Society of Toxicology. The Great Blizzard of 1993 did do some damage to the meeting program–about 300 registrants failed to show, including key speakers in sessions on dioxin science and "space toxicology." But toxicologists rebounded later in the week with a special "snow delay poster session" and a debate on regulatory approaches to dioxin. Also of topical interest: a pair of sessions on the health effects of breast implants and lead.

Lead Still a Threat Abroad

Less and less leaded gasoline and paint is making its way onto the U.S. market these days, but that doesn't mean the health threat from lead has disappeared. On the contrary, there's still plenty of it around—particularly in other countries. For that reason, some epidemiologists studying the health effects of lead are beginning to conduct their research abroad. In one session at the toxicology meeting, epidemiological studies done in the former Yugoslavia and Egypt provided new evidence of lead's health effects on children's mental performance as well as a possible link between lead and infertility.

These days, lead poisoning may be the least of people's worries in what remains of Yugoslavia, but in a study launched in 1985—before the civil wars began—a team led by Columbia University pharmacologist Joseph Graziano looked at the effects of lead on the cognitive ability of children. The group recruited pregnant women who lived either near a lead smelter in Kosovska Mitrovica, Serbia, or in a "non-lead-exposed town" 25 miles to the south. So far, the researchers have followed 334 children from birth to 4 years of age, controlling for several possible confounding variables, including the mother's age and the children's intelligence, birthweight, and gender. Unlike in past epidemiological studies, Graziano's group also controlled for hemoglobin levels, because iron-deficiency anemia has been linked to cognitive impairment.

Graziano's group found what he calls a "striking" dose-response relationship between blood lead levels and a standardized measure of cognitive function called the General Cognitive Index (GCI). The researchers saw a gradual decrease in GCI scores as the blood lead levels increased. Graziano's study adds ammunition to a camp that has argued for years that lead exposure is responsible for slight changes in GCI scores and other measures of intelligence in children. But the clinical significance remains debatable. "For a given individual it's hard to say what the consequences are. For society as a whole, if we lose 3 to 5 IQ points or more, we'll have more people who fulfill the definition of being mentally retarded who will need a special education," Graziano says.

Chronic health effects of lead poisoning, as seen in the Yugoslavian children, are hard to detect in adults. That's why epidemiologists have begun screening for such damage in adults who live in countries with heavy lead pollution. Egypt fits that bill. In Cairo, for example, the ambient air concentration of lead is 3 milligrams per cubic meter (mainly from leaded gasoline), about 1000 times higher than U.S. levels.

To test the effect of such high levels of lead exposure on Cairo men, a team of Cairo University researchers led by toxicologist Ashraf Youssef studied the semen of 30 infertile men and 25 fertile men. About half the men had extra lead exposure from their work as "traffic soldiers." The researchers found that whereas the average sperm count in fertile, nonoccupationally exposed men was about 70 million per millileter, in the most severely affected traffic cops it was 7 million per milliliter. The percentage of abnormally shaped sperm also increased in the lead-exposed group.

While the Egyptian findings are suggestive, lead-induced changes in sperm function are much harder to detect in the United States and other countries that experience less lead pollution. That's why epidemiologists are searching for biomarkers that might reveal physiological changes induced by tiny amounts of lead. One possibility is the widely used sperm chromatin structure assay. At the session, University of Washington graduate student Tim Ewers reported that in rats with blood lead levels roughly that of occupationally exposed U.S. men, the assay flagged changes in the proportion of certain sperm precursor cells produced in the testes. Washington toxicologist Elaine Faustman suggests that altered levels of precursor cells might decrease the number of sperm available for reproduction. "We have a lot more work to see if that's true," she says.

The Case Against Implants

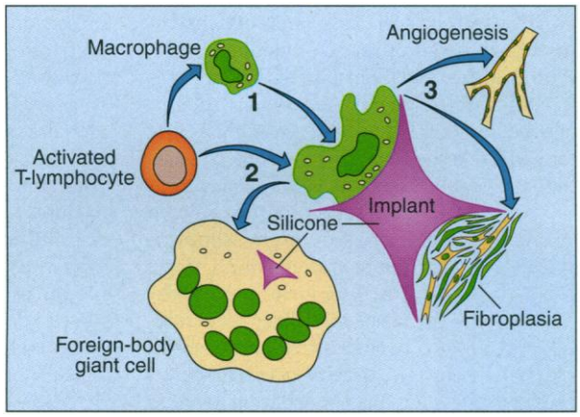
Many of the roughly 1 million women who have silicone breast implants recall suffering from fatigue, achy joints, and swollen lymph nodes. These are classic symptoms of immune dysfunction. But they're also classic symptoms of the flu and other common maladies, which makes it hard for epidemiologists to pin down cause and effect. Nevertheless, the Food and Drug Administration (FDA) last year decided that the evidence was strong enough to order silicone-filled implants off the market. That decision seemed to be on firmer ground last week. New results presented at the annual meeting and in two papers published a few days later indicate that materials used in many implants can evoke an immune response in animals.

One of the studies examined the health effects of polyurethane, a polymer used to encapsulate many implants. Past studies have shown that polyurethane-coated implants release small quantities of a carcinogen called 2-toluenediamine. A group led by National Cancer Institute pathologist Sabine Rehm reported at the meeting that it has developed a mouse model that mimics the local effects of polyurethane-coated breast implants. After surgically inserting discs of polyurethane foam in mice, the researchers saw inflammation in surrounding connective tissue that appeared similar to that seen in women with implants. Rehm's study will appear in an upcoming issue of *Toxicologic Pathology*.

The second study reported at the meeting focused on the silicone gel that gives some implants their shape. With funding from the National Toxicology Program, a team led by Albert Munson, a toxicologist at the Medical College of Virginia in Richmond, studied the immune response of female mice injected with silicone gel. Munson said the mice had reduced levels of activity of natural killer cells, which kill tumor cells but are under different genetic control from immune cells. Moreover, the activity decreased as the dose of silicone increased. But the results are hard to interpret because these mice appeared otherwise healthy, Munson says.

Silicone gel made headlines again last month when researchers at Rochester General Hospital found that the gel might potentiate an immune response in rats. In a study published in the March issue of *Immunological Investigations*, a group led by Rochester immunologist John Naim found that rats injected with silicone gel were far more likely to mount an antibody response to a cow protein than rats injected with saline. This "adjuvant effect" was first posited for silicone in a 1964 Japanese paper, but research on it lay dormant for years. "We went ahead and did a study that should have been done years ago," Naim says.

Indeed, in 1974 the Dow Corning Corp., at the time a manufacturer of silicone-filled breast implants, found that several silicon-containing compounds possessed adjuvant activity. "We saw a response, but we didn't think it meant anything," says Robert LeVier, Dow's director of bioscience research. Lori Love, an FDA pathologist, says the Dow study could easily have been dismissed in light of the scant knowledge about adjuvant effects 20 years ago. Still, FDA commissioner David Kessler believes that Dow should have followed up its study sooner. "It's an unqualified yes that there should have been more care taken," Kessler told *Science*, because "their own people were raising significant safety questions." Dow got wind of Naim's investigation last year and replicated it. The results were virtually identical. "This is fairly hot news," LeVier says. "But we're still not sure what the heck this means."



SOURCE: SABINE REHM ILLUSTRATION: C. FABER SMITH

A cellular cascade. This is a composite of the latest theories on how silicone-filled breast implants might trigger a chronic inflammatory response. (1) Macrophages, cells that gobble up foreign material, swarm over the surface of an implant; (2) Stimulated by activated T-lymphocytes, some macrophages fuse to form foreign body giant cells that engulf beads of silicone gel; (3) Macrophages release substances that lead to growth of blood vessels near implant (angiogenesis) and scar tissue around implant (fibroplasia).

Dioxin: Still Deadly

For years the Environmental Protection Agency (EPA) held that dioxin was so dangerous that human beings shouldn't be exposed to it at all. But that picture became clouded in the 1980s when molecular biologists identified the cellular receptor to which dioxin binds. The possibility that it may take a certain number of dioxin molecules to activate its receptor (and a certain number of receptors to cause a harmful effect) forced a rethinking of EPA's assumption that even a single molecule of dioxin could be harmful. Based on emerging data about the dioxin receptor, in 1991 EPA launched a reassessment of the chemical's health risk. Now the assessment is nearly finished and at the annual meeting, EPA's top dioxin researcher, toxicologist Linda Birnbaum, sketched out where the agency stands on dioxin. In what would be a return to EPA's original position, Birnbaum suggests that dioxin's status as a health threat is unchanged. "In my opinion, there is no reason to believe that dioxin is less hazardous than had been presumed in the past," she told *Science*.

Ulf Ahlborg, a toxicologist at Sweden's Karolinska Institute, echoed Birnbaum's caution. The data, he said, "don't support the idea of a general threshold for dioxin's effects." The reason: Toxicologists believe that dioxin receptors—known as Ah receptors—may vary in their function, depending on the tissue they're found in. What also might alter an organ's susceptibility to dioxin is that the compound, in rodents at least, winds up getting deposited preferentially in certain tissues. In a poster session, Birnbaum's lab described such findings in mice, in which dioxin added up quickly in the thyroid, adrenals, skin, liver, and fat.

That's only one factor in Birnbaum's hesitancy to paint dioxin as being any less sinister than the EPA originally thought. Understanding the role of the Ah receptor has led the EPA to broaden its framework and look for a cumulative dioxin-like effect caused by chemicals that also wreak their havoc by binding to this receptor. Birnbaum, who works at EPA's health effects research laboratory in Research Triangle Park, says the EPA is assigning "toxic equivalency factors" (TEFs) to those dioxin-like chemicals. The agency now estimates that the U.S. population, on average, has 7 parts per trillion (ppt) of dioxin circulating in the blood. But after assigning TEFs to the related agents, among them chemicals called dibenzofurans, the estimate jumps to an equivalent of 30 ppt of dioxin-like chemicals in blood. Throw in some of the PCBs, which also exert their effects on the Ah receptor, and the estimate rises to fifty ppt. "Fifty ppt is a level we should be concerned about," Birnbaum says.

Birnbaum declined to speculate on whether EPA administrator Carol Browner will keep the dioxin standards tight based on the new approach, and Ahlborg was equally noncommittal about European regulations. But it is clear that the risk assessment report will reflect these new unsettling findings when it lands on Browner's desk this fall. And then she must decide whether dioxin should remain classified as one of the most dangerous known environmental pollutants.

–Richard Stone