that humans and rodents are similar in the way they process PP chemicals, that could make health officials more concerned.

There's no evidence at present of any similarity in human and animal responses. But the discovery that PPs are involved in a poorly understood receptor system is reason for concern in its own right. Any chemical that triggers cellular events like those dioxin triggers is going to raise eyebrows—particularly if the chemical is spread as widely through the environment as PPs are.

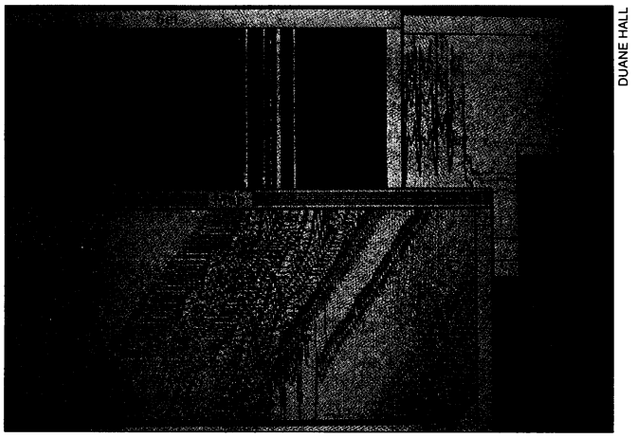
Marsman reports that last year, EPA started the ball rolling on a new research program in this area. EPA headquarters asked NIEHS to investigate one of the phthalates as a hazardous air pollutant. This means that the entire class will come under scrutiny, and we can expect to hear a lot more in the future about peroxisome proliferators.

What is the bottom line?

The movement toward molecular methods within toxicology isn't being accomplished without stress. Some traditionalists feel the new toxicology is "reductionist," as Gallo says, in its fine-grained focus on events within the cell. John Doull, emeritus professor of toxicology and pharmacology at the University of Kansas Medical Center and co-editor of one of the essential texts in the field, says the new biology fascinates him—but he worries about its applicability. "We get a lot of groups doing molecular toxicology for its own sake," but sometimes people "fail to relate it to the whole animal," says Doull. And if it lacks context, he worries, it may lose touch with toxicology's ultimate goal—protecting public health. Gallo concedes that the focus often seems to have narrowed, but he argues that "we are actually broadening our thought patterns at the other end" by describing fundamental biological mechanisms that underlie many toxic effects.

Most leaders in the field of toxicology believe, as Roger McClellan, president of CIIT says, that molecular biology is enabling officials to "get smarter in using animal data" in assessing the risks of exposure to chemicals. And he points to a small victory last year that may prove to be a blessing for gasoline makers. EPA accepted on its scientific merits the argument that a particular type of animal tumor—one produced in male rat kidneys by chemicals binding to a protein called alpha 2 micro globulin—should not be viewed as evidence of carcinogenic risk for humans. This message—the first of its kind, NIEHS scientists say—has now gone out from headquarters to all EPA toxicologists. That may be good news for sellers of unleaded gasoline, which induces male rat kidney tumors.

The benefits of molecular toxicology are spreading to other areas—for example, to drug companies' labs, says Jeffrey Theiss of the Warner-Lambert Co. Instead of methodically running a series of slightly similar compounds through the same battery of animal tests, says Theiss, "now the emphasis is more on understanding the molecular biology of a particular disease...and we can rationally select targets... [and] develop agents that can disrupt the process." For example, he mentions that the lab has developed a special culture of adrenal cells to precheck compounds before testing them in vivo.



DUANE HALL

Toxic wizardry. NIEHS's automated DNA sequencer projects a lung tumor gene on the screen.

At the M.D. Anderson Center, Walker has developed a series of molecular tests to yield an index of toxicity without resorting to expensive animal studies. Consider a company, Walker says, that wants to develop a new, safe substitute for asbestos. Before making a big investment, the technical staff would consult a group like her own to learn how to target the toxicology studies to get the best information on potential lung effects. She might even help them set up the assays to run in parallel with product research.

Small improvements like these mean a lot to enthusiasts—like Gallo—who insist that toxicology stands at the beginning of a new era. In the future, they say, big decisions will be based more on an understanding of toxic mechanisms and less on rigid mathematical models based on dose response curves derived from animal models. Gallo says the shift will "shake a lot of trees," and "people will get nervous." But he argues that changes brought about by the molecular revolution will be good for everyone—if for no other reason than that they will bring more fundamental science into the debate.

–Eliot Marshall

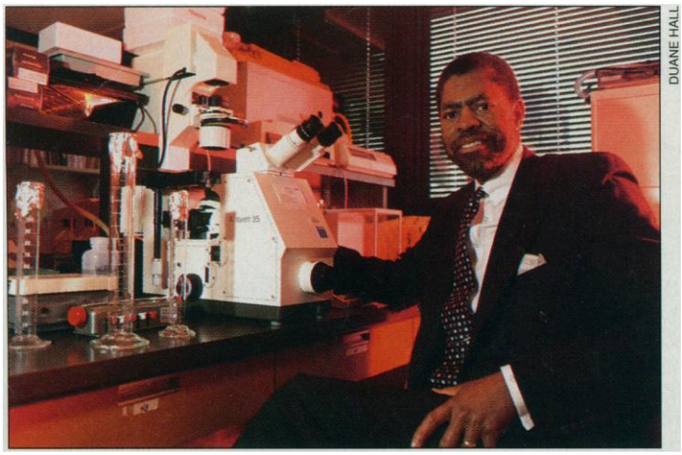
INSTITUTIONAL PROFILE

Ken Olden Heals NIEHS's 'Split Brain'

When cancer researcher Kenneth Olden left his job as director of Howard University's Cancer Center to become director of the National Institute of Environmental Health Sciences (NIEHS) in June 1991, he inherited a 25-year-old organization with a split in it that resembled the one between the hemispheres of a human brain. The creative, synthetic "right brain" was the division of intramural research, which carried out basic research into epidemiology and toxicological mechanisms. The analytical, linear "left brain" was the National Toxicology Program (NTP), which carried out routine animal tests of potentially toxic substances. Every brain needs these faculties working in tandem, but, like a brain in which the corpus callosum doesn't function well, the halves of NIEHS communicated poorly over the years, says an institute official, and "a deep gulf developed between the people" in each half—leaving the nation's top toxicology center with a dissociated sense of its own mission.

Olden knew a key to success in his new role was getting the halves of his agency to think in sync. And whether he succeeded or failed would have significant consequences for the field of toxicology, because NIEHS (a part of the National Institutes of Health (NIH) located in Research Triangle Park, North Carolina) is the government's main toxicology center, spending $150 million on research every year, more than any other federal entity. But when Olden came on board, the agency, created as a division of NIH in 1966 and elevated to institute status in 1969, was perceived to be slipping in its leadership role, coming under criticism from Congress and environmental groups for testing fewer toxic chemicals each year. Under those circumstances, it was tough to persuade Congress to add to the institute's research budget—something researchers there wanted badly.

Confronted with a divided institute hard up for cash, it didn't take long for Olden to realize he needed to make major changes in the shape of his institution. Although the 54-year-old cell biologist from Parrottsville, Tennessee, had little experience in environmental research, he didn't hesitate to order up a reorganization. "I want to get toxicologists talking to and collaborating with molecular biologists, epidemiologists, and pharmacologists," Olden told *Science* in a recent interview. To do that, the new director broke down the rigid institutional barriers between



DUANE HALL

Mover and shaker. Shortly after his arrival at NIEHS, Ken Olden ordered a major reorganization.

the halves of the organization and put all the institute's researchers into one unit under scientific director John McLachlan.

That kind of reorganization meant challenges for both the left brain and the right brain at the institute. For the toxicology program, created by Congress and added to the institute in 1978, the challenge meant incorporating some of the cutting-edge molecular biological approach that is taking over toxicology (see page 1394). The need for that kind of change came through loud and clear in the report of a panel of outside scientists Olden convened in April 1992 to evaluate NTP. Last July, the panel reported that NTP "places too much emphasis on testing per se" and not enough on understanding the underlying mechanisms, a type of knowledge "required for a realistic interpretation of the significance of the testing results with regard to human health."

But as at other established institutions, changing ingrained habits isn't going to be easy. Says NIEHS dioxin researcher George Lucier: "People get in habits that are hard to break. Many [NTP] scientists are trained as classic toxicologists, and have little mechanistic background." For these scientists, he says, Olden's reorganization "can be a difficult adjustment."

The classical toxicologists of the NTP, however, aren't the only ones who face challenges. Over on the other side of the institute's brain, NIEHS researchers face the hurdle of overcoming a fascination with the exotica of cancer research and an accompanying distaste for the nitty-gritty of toxicology and applied science, patterns that are built into their side of the institute's culture. Indeed, in the early days, NIEHS was known as "NCI South," a jibe at a research program that seemed a copycat version of the one at the National Cancer Institute (NCI) in Bethesda, Maryland. In those days, "people [at NIEHS] said they didn't want to be viewed as toxicologists, or like people at the EPA," says a veteran toxicologist who has divided his career between academia and industry.

One theme of Olden's young directorship has been shedding that "NCI South" reputation. Olden wants NIEHS to conduct more research on noncancer endpoints—how environmental substances contribute to reproductive problems such as premature birth and infertility, and to neurological disorders such as Parkinson's disease. "We really need to address those as aggressively and as vigorously as we do cancer," he says. In addition, Olden wants to steer the institute toward preventing environmentally induced diseases. Olden has a two-pronged approach for this: increase the number of studies on mechanisms by which chemicals act in humans and launch clinical trials of promising interventions. "I'm very impressed with how he's moving NIEHS to preventive efforts," says Rutgers environmental scientist Bernard Goldstein.

Olden hopes that it will be possible, for example, to find ways of blocking the effects of dioxin and aflatoxin. And under his guidance, NIEHS is already setting up its first large-scale, formal trial to study the efficacy and safety of a new compound for treating lead poisoning. Walter Rogan, the NIEHS epidemiologist who's coordinating the lead study, says it will compare the effectiveness of two chelating agents to remove lead from children's blood. One (EDTA) is already in use, and the second, Succimer (dimercaptosuccinic acid), is being considered as an alternative. Succimer appears to have some big advantages over EDTA. First, it's given orally, while EDTA needs to be injected. Second, Succimer seems to bind to lead more than other metals, including zinc and calcium, which the body needs. EDTA, meanwhile, seems to be less selective. And Rogan says the nation needs to be prepared for a potential growth in demand for Succimer now that research is showing that lead is toxic to the nervous system at lower blood levels than previously thought. Rogan estimates that 800 children will be enrolled in the trial, starting in June 1994.

Though Olden gets high marks from many for his ambitious plans, he hasn't had much success getting the new programs funded. The NIEHS's $250 million budget for 1993 is virtually unchanged from last year's budget. Olden says his top priorities would require $600 million in funding. But in view of the overall federal budget crunch, the prospect of a more than 100% budget increase for 1994 is extremely unlikely. As a result, Olden says, NIEHS top brass are combing the institute for expendable programs that "aren't likely to have a significant impact on human health," he says.

Despite the budgetary problems, Olden is getting good reviews from outside the institute. Last year, says Goldstein of Rutgers, "I spent a lot of time answering phone calls from people who were upset with the reorganization." Now, he adds, "I'm no longer hearing any complaints." John Emmerson, an Eli Lilly & Co. toxicologist and president of the Society of Toxicology, says, "I'm impressed by the guy," and adds, "he's trying to make sure the NTP is on a course consistent with good science." High praise for a newcomer to the field. But it remains to be seen how well Dr. Olden's prescription for the split between NIEHS's divided hemispheres will work over the haul.

–R.S.

Further Reading

"Toxicology Goes Molecular"

Melvin E. Andersen *et al.*, "Modelling Receptor-Mediated Processes With Dioxin: Implications for Pharmacokinetics and Risk Assessment," *Risk Analysis*, in press.

Thomas R. Sutter *et al.*, "Targets for Dioxin: Genes for Plasminogen Activator Inhibitor-2 and Interleukin-1B," *Science*, 18 October 1991, p. 415.

"A Breath Test for Cancer?"

George H. Lambert *et al.*, "The Caffeine Breath Test and Caffeine Urinary Metabolite Ratios in the Michigan Cohort Exposed to Polybrominated Biphenyls: A Preliminary Study," *Environmental Health Perspectives* **89**, 175 (1990).

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