

# NIEHS News

## Succimer Gets TLC

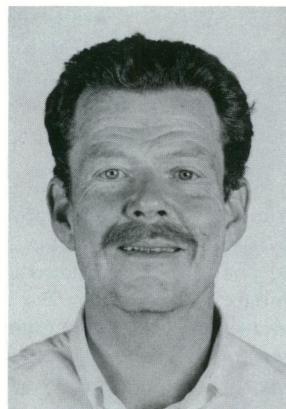
Kenneth Olden, director of NIEHS, and John Ruffin, director of NIH's Office of Minority Health Research, have announced the signing of five contracts for a 5-year clinical trial of succimer, a drug that reduces blood lead levels in children. The purpose of the trial is to determine whether treating children with relatively low blood-lead levels prevents or reduces associated developmental delay and whether the drug is safe.

Walter J. Rogan is the project officer for the trial, and the coordinating center will be at Harvard University, with James Ware as principal investigator. The other principal investigators and clinical centers are 1) Frances M. Gill of Joseph Stokes, Jr. Research Institute, Children's Hospital of Philadelphia, 2) Julian Chisolm of Kennedy-Krieger Research Institute, Inc., in consortium with Johns Hopkins University and University of Maryland at Baltimore, 3) Richard P. Wedeen of the University of Medicine and Dentistry of New Jersey, and 4) Robert L. Bornschein of the University of Cincinnati.

Each of the centers will treat about 250 children 18–24 months of age and follow them for up to 4 years. All children will have the lead dust and paint in their homes cleaned up and will receive vitamin and mineral supplements so they meet current recommended daily allowances, especially for zinc and calcium. The Toxicity of Lead in Children (TLC) clinical trial will cost approximately \$30 million over the next 5 years.

Recent studies of lead-exposed children show that blood-lead levels once thought to be harmless cause significant delays in motor control and intellectual development. These developmental delays may impede social development and readiness for school. The TLC trial will determine if succimer reduces or eliminates such developmental delays.

Succimer is a relatively new drug that has not been adequately tested clinically. It is the first available drug of its type (a



**Walter J. Rogan**, project officer for the TLC Trial

chelating agent) since 1950, and it can be orally administered at home. Succimer appears to be relatively safe and may not cause as much loss of elements needed by the body, such as zinc and iron, as do other drugs.

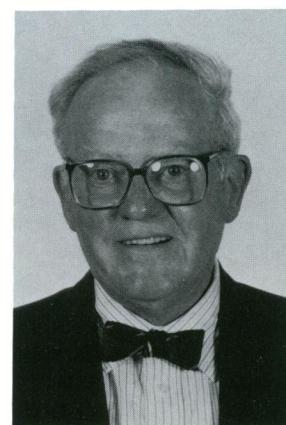
The TLC trial is made possible through an agreement between NIEHS and the Office of Research on Minority Health, which allocates \$5 million per year for five years to address minority

health concerns related to the environment. The agreement was signed in March by Olden and Ruffin.

"This clinical trial could have tremendous impact on the health of minority children. Lead poisoning is just one health concern that disproportionately affects minorities. By joining forces on this issue and others, the ORMH and the NIEHS are working to reduce the burden of illness shouldered by minority Americans," said Ruffin.

In a recent article in *Preventive Medicine*, Olden noted "Children ingest their environment. When that environment is contaminated by lead, they ingest lead. They absorb and transport lead across their gastrointestinal tracts and into their bloodstreams about six times more efficiently than adults do. A major environmental health issue for children today is the extremely high prevalence of unacceptable exposure to lead, especially in inner cities,

but occurring throughout the country. This clinical trial will address the terrible toll lead takes on our children's futures."



**J. Julian Chisolm**, Kennedy Krieger Research Institute



**James H. Ware**, Harvard University

scientists and other professionals from all over the world met at NIEHS, home base of the NTP, to review 10 separate attempts to predict rodent bioassay results.

The purpose of the workshop, "Predicting Chemical Carcinogenesis in Rodents," was to assess prediction methods. If carcinogenicity could be predicted, chemicals could be prioritized for study and warnings issued for exposure to certain chemicals until cancer studies could be done. In the first part of the workshop, participants gave overviews of the methods they used to make predictions. In the second part of the workshop, organizations that use study results (regulatory agencies, research institutions, etc.) discussed the strengths and weaknesses of the various methods. In a summary of the workshop, Michael Shelby of NIEHS gave an overview, citing both the positive aspects of the prediction methods and the

many hurdles yet to be overcome.

Shelby pointed out that there were at least three strengths evident in the prediction efforts. First, some of the systems described at the workshop were successful in predicting strongly carcinogenic chemicals and some clearly noncarcinogenic chemicals; second, the systems performed better with certain classes of chemicals; and finally, all the systems have the potential to be improved.

A major problem in optimizing the performance of the various prediction methods is the lack of detailed information on mechanisms of carcinogenicity. An understanding of the bioavailability of a given chemical, as well as possible changes in the metabolism of the chemical during aging, would be beneficial in predicting carcinogenicity. Likewise, improvements in the ability to monitor early events in the carcinogenic process such as genetic instability, changes in gene expression, and activation of oncogenes would help establish structure-activity relationships. Researchers at the workshop were optimistic about the continued evolution of methods to predict a variety of biological activities.

Other issues confronted in the workshop included changes in tumor rates of control animals over time, the unknown reproducibility of most rodent bioassays, and the fact that most models used in the