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rological disorders, immune dysfunctions and other chronic diseases.

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Opportunities now exist for studies of genetic susceptibility for cancer and other diseases in which an environmental component can be presumed. Environmental factors contribute to many of the disease processes that are specific to or predominate in women. For example, heavy metals have been shown to accelerate osteoporosis, a bone disorder affecting most women over age 60.

A number of widespread environmental toxins such as DDT and the PCBs mimic the female hormone estrogen and can play a role in hormonally related cancers such as those of the breast, the uterus and the ovaries. Environmental estrogens could also be important components of benign proliferative disorders of the female reproductive tract such as endometriosis and uterine fibroids.

Many environmental compounds affect reproduction, leading to infertility, premature birth or birth defects.

Similarly, children's health is also a priority of the National Institute of Environmental Health Sciences. The developing fetus and infant represents particularly vulnerable targets for environmental agents, and adverse effects sustained at this time can cause health problems throughout the individual's life. These problems may even be apparent many years after the original exposures.

Finally, greater emphasis has been assigned to human studies with the development of a clinical program.

The NIEHS has started several new clinical research activities. One is a multi-center project, which will examine the efficacy of the oral chelator succimere, to treat children with low blood lead levels. Another program will make use of local medical centers in the Raleigh–Durham area to mail their clinical research with the laboratory research ongoing at NIEHS.

Initial studies will look at environmental factors that promote asthma, dysfunctions of reproductive endocrinology, and the degenerative neurological diseases, hazard identification and characterization.

Use of traditional animal tests and epidemiologic studies to identify environmental hazards to human health will remain a cornerstone of the Nation's prevention intervention program at NIEHS. The strategy of these techniques will be greatly improved with incorporation of new insights concerning the molecular basis of toxic effects into animal testing and human epidemiologic studies.

However, animal studies often provide only descriptive information, revealing the toxicity of an environmental agent by its ability to cause effects such as tumors, histopathologic abnormalities or genetic chance.

An even more meaningful way to relate animal studies to human health effects is by determining the underlying mechanism leading to toxicity. Hazard identification is often handicapped by our in-

responsiveness, and understanding the ability of environmental chemicals to interact with these critical proteins is an important NIEHS research priority. Research in this area holds promise for defining the roles that environmental agents may play in a host of diseases and dysfunctions, including infertility, birth defects, neurological disorders, immune dysfunctions, and chronic diseases.

The variation in individual response to environmental agents is exceptionally wide. This variation is accounted for by differences in metabolism, DNA repair capacity, or genetic predisposition to specific diseases. It is because of this large diversity in responsiveness to environmental toxicants that risks to environmental agents have been difficult to pinpoint, particularly at low exposures. Opportunities now exist for studies of genetic susceptibility for cancer and other diseases in which an environmental component can be presumed.

Of particular interest to the NIEHS are environmental components of women's, children's, and minority health. Environmental factors contribute to many of the disease processes that are specific to, or predominate in, women. For example, heavy metals have been shown to accelerate osteoporosis, a bone disorder affecting most women over age 60. A number of widespread environmental toxicants such as DDT and PCBs mimic the female hormone estrogen and could play a role in hormonally related cancers such as those of the breast, uterus, and ovaries. Environmental estrogens could also be important components of benign proliferative disorders of the female reproductive tract, such as endometriosis and uterine fibroids. Many environmental compounds affect reproduction, leading to infertility, spontaneous abortion, or birth defects.

Similarly, children's health is also a priority of the NIEHS. The developing fetus and infant represent particularly vulnerable targets for environmental agents. An adverse effect sustained at this time can cause health problems throughout an individual's life. These problems may not even be apparent until many years after the original exposure.

Finally, greater emphasis has been assigned to human studies with the development of a clinical program. The NIEHS has started several new clinical research programs. One multi-center project will examine the efficacy of an oral chelator, succimer, to treat children with low blood lead levels. Another program will use local medical centers to meld their clinical research with the laboratory research ongoing at NIEHS. Initial studies will look at environmental factors that promote asthma, dysfunctions of reproductive endocrinology, and degenerative neurological diseases.

Hazard Identification and Characterization: Use of traditional animal testing and epidemiologic studies to identify environmental hazards to human health will remain a cornerstone of the Nation's prevention and intervention program. The strength of these

Dr. Olden. These efforts are funded through both extramural and intramural mechanisms.

Mr. Stokes. How much is included in the FY 1995 budget request for this effort?

Dr. Olden. These efforts account for approximately $2.5 million of the FY 1995 budget request.

LEAD POISONING

Mr. Stokes. The "Lead in Children" Clinical Trial. How is this clinical trial progressing?

Dr. Olden. The planning phase of this clinical trial, which is known as the Treatment of Lead-exposed Children, is almost complete, and the protocol is now at FDA. This is a multi-center, randomized, placebo controlled trial that is attempting to show whether oral chelation therapy, in addition to vitamin and mineral supplementation and home clean-up, is a safe and effective way of preventing lead-induced delays in cognitive development, altered behavior, and slowed growth. We plan to enroll about 1,300 (total) children from Columbus, Cincinnati, Philadelphia, Baltimore, and Newark, treat them when they are between 12 and 32 months old, and follow them for about three years. We hope to treat the first child in August, and enroll all the children by September, 1995.

Mr. Stokes. Are there "Lead Poisoning Prevention" programs underway in this area? Explain.

Dr. Olden. All of these cities have some kind of lead poisoning prevention program. The clinical facilities we are using for the trial usually serve a the medical referral site for children found to have elevated blood lead levels.

Mr. Stokes. In your professional judgment, what is needed most to address the lead poisoning problem?

Dr. Olden. Lead poisoning is an entirely preventable disease. People should not be exposed to leaded environments, but for millions, where they live is either unavoidable due to limited income or chosen occupation such as farming or specifically chosen location such as the "yuppies" moving back into a renovated inner city. However, lead safe housing for everyone is probably at least a generation away. In the meantime, we need to screen children, and we need to have sound, reliable data on safe, effective intervention methods for dealing with children whose lead levels are too high.

Mr. Stokes. Of these needs, which do you consider to be the most pressing unmet need?

Dr. Olden. We view the need to screen children, and to have sound, reliable data on safe, effective intervention methods for dealing with children whose lead levels are too high as the most pressing needs.

Finally NIEHS, through the minority supplements to research grants program, currently supports eight Hispanic individuals at the undergraduate and pre-doctoral level.

Mr. Serrano. Fourth, what is your Institute doing to recruit and retain more Hispanics for clinical trials?

Dr. Olden. The NIEHS has only one external clinical trial program at this time. This initiative, the Institute's first, is a five-year clinical trial to determine the efficacy of succimer, a lead chelating agent, in reducing the elevated blood lead levels of children living in five inner city areas. In one of the participating centers, Newark, New Jersey, the population of children is 23% Hispanic. The clinical trial relies on referrals from health care providers to enroll children in the program. Retention is promoted through assurances that houses will be cleaned and children will receive vitamins and other medical care as well as incentives such as T-shirts, balloons, and hats. The portion of this project dealing directly with Hispanics will cost approximately $2 million over five years.

Mr. Serrano. Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators, how their success rate compared to the Institute's overall success rate, and whether there is an explanation for any disparity in these success rates.

Mr. Stokes. What is the estimated cost of the research needs to address the most pressing unmet need?

Dr. Olden. The cost of the treatment of lead-exposed children clinical trial is expected to be approximately $29 million. We need new ways to approach the problem of exposure of the fetus to lead, because we know that damage occurs there. The requirements for safety of any intervention during pregnancy, however, are very stringent. At a more basic level, we need to know more about how lead affects the developing brain, when those effects are permanent and when they are reversible, and how we can reverse them.

ENVIRONMENTAL HAZARDS AND BREAST CANCER

Mr. Stokes. How much more do we now know about the effects of environmental hazards on the development of breast cancer than we did five years ago and how much closer are we to unraveling the relationship?

Dr. Olden. In the last five years we have become more confident about certain risk factors that are likely involved in breast cancer. However, other than genetic predisposition, which cannot account for the enormous numbers of women with breast cancer, consensus etiological risk factors have yet to be fully deciphered. Most scientists in this field would agree that we have now a reasonably good idea about possible risk factors of breast cancer, which include: genetic susceptibility/inheritance; early age of menarche; age of first full-term pregnancy; lactation; late menopause; dietary fat and diet per se; and environmental agents. Nearly 40 of the 450 agents we have so far studied for possible cancer in laboratory animals have been identified as causing cancer of the mammary glands. Including other research organizations that have done bioassays, about 75 of the 1000 agents studied adequately have been identified as causing cancer of the mammary glands in animals. We have reported these findings at the May 1994 meeting of the American Association for Cancer Research.

Those chemicals with convincing evidence of cancer in animals and that exhibit exposures to humans should be investigated as possibly implicated in the steady rise in incidence of breast cancer. Epidemiological studies will have to be done to confirm these findings in exposed populations.

Just recently several research reports have implicated certain chlorinated organo-halogenated-hydrocarbons, for example, pesticides, as being linked to increased risks of breast cancers. These chemicals include DDT, and certain metabolites, and lindane.

Long-term collaborative efforts at our Institute have allowed us to consider estrogens, endocrine-disrupters, and so-called xenoestrogens in the environment as representing potentially major sources of hormonal body burdens that may be associated with increased cancer risks. So we are making progress on a number of fronts. New developments into area of genetics occur almost daily and we are gaining a greater understanding of the mechanism by which environmental factors cause disease. It is in understanding this

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potentially lead to the design of a more effective drug that the virus cannot escape.

ELECTROMAGNETIC FIELDS

Mr. Dickey: What advancements have been made in the past year in your animal studies regarding prolonged exposure to electromagnetic fields?

Dr. Olden: The preliminary findings from our toxicologic study are currently undergoing peer review. We will report these findings at the meeting of the Bio-Electric Magnetics Society in Boston in June. I cannot give you a detailed report at this time but I have reviewed this information and we are not finding any health effects in these animal studies that would give rise to concerns about adverse effects in pregnant women or their babies which has been one of the major worries in this area.

Mr. Dickey: What have your studies of electromagnetic fields concluded regarding the use of advanced telecommunication and computing devices, such as cellular phones and personal desk-top computers?

Dr. Olden: NIEHS is not conducting any research directly related to possible health effects from these exposures. Congress specified that our research involve the magnetic fields produced by the transmission and use of electrical current in the 60 hertz frequency range. However we are consulting with the National Institute of Occupational Safety and Health. They have not found any significant health effects from exposure to video display terminals in the work place in their study. The National Cancer Institute is conducting a very large epidemiologic study of risk factors in brain cancer and has included research into the effects of cellular phones in this study. The results of their study are several years away.

LEAD CLINICAL TRIAL

Mr. Dickey: How is the "Lead in Children" Clinical Trial progressing?

Dr. Olden: The recruitment phase of the clinical trial, which we call the Treatment of Lead-exposed Children, or TLC, Trial, has been underway since late last summer, and as of March 20, 1995, 102 children had begun treatment. This is a multi-center, randomized, placebo controlled trial that is attempting to show whether oral chelation therapy, in addition to vitamin and mineral supplementation and home cleanup, is a safe and effective way of preventing lead-induced delays in cognitive development, altered behavior, and slowed growth. We hope to enroll a total of 1,300 children from Cincinnati, Philadelphia, Baltimore, and Newark, treat them when they are between 12 and 32 months old, and follow them for about three years.

ASTHMA

Mr. Stokes: Asthma continues to be a major medical problem effecting 10 million Americans, more than one-third of whom are under 18 years of age. Studies reveal that African Americans and Hispanics living in inner-city areas may have unusually high rates of asthma morbidity and mortality. To what extent are researchers supported by your Institute conducting research in this area?

Dr. Olden: The National Institute of Environmental Health Sciences (NIEHS) has a historical commitment to studying the basic scientific relationships between air pollutants and lung dysfunction and disease. We have joined with the National Institute of Allergy and Infectious Diseases (NIAID) in the National Cooperative Inner-City Asthma Study. The goal of this study is to design and evaluate asthma intervention strategies in underserved, inner-city children from 4 to 12 years of age. The NIEHS is focussing its efforts in this study on the environmental components of the intervention plan. If this intervention study is scientifically successful, the NIEHS will be in a strong position to develop a focussed program initiative directed toward understanding the mechanisms involved in the etiology of respiratory dysfunction from exposure to indoor environmental agents. A recent Program Announcement issued jointly by the NIEHS, NIAID and the National Heart Lung and Blood Institute will stimulate research to understand the mechanisms by which air pollutants exacerbate and contribute to asthma morbidity and mortality.

Mr. Stokes: What have we learned about the environmental factors associated with asthma since you were here last?

Dr. Olden: We have a rich abundance of positive data to link exposure to environmental agents, such as ozone, sulfur dioxide, particulates and acid aerosols, to increases in the prevalence of respiratory symptoms in children and adults. These studies have revealed that asthma appears to be exacerbated in those children with preexisting conditions, such as clinically diagnosed asthma, following exposure to outdoor air pollution. The indoor environment has also been a recent focus of interest, especially as individuals spend most of their life indoors. Elements in the indoor environment have been associated with asthma, such as house dust mites, cockroach, cat dander, tobacco smoke and nitrogen dioxide.

LEAD POISONING

Mr. Stokes: What is the status of the "Treatment of Lead Poisoning in Children" clinical trial?

Dr. Olden: The recruitment phase of the clinical trial, which we call the Treatment of Lead-exposed Children, or TLC, Trial, has been underway since late last summer, and as of March 20, 1995, 102 children had begun treatment. Study procedures have been very acceptable to the families involved, but recruitment has been slower than we had anticipated. This is a multi-center, randomized, placebo controlled trial that is attempting to show whether oral chelation therapy, in addition to vitamin and mineral supplementation and home cleanup, is a safe and effective way of preventing lead-induced delays in cognitive development, altered behavior, and slowed growth. We still hope to enroll about 1,300 children from Cincinnati, Philadelphia, Baltimore, and Newark, treat them when they are between 12 and 32 months old, and follow them for about three years. We are now planning to extend enrollment to September 1996.

Mr. Stokes: What other significant research is underway at your Institute to address environmental related diseases in children?

and individuals at this conference are being used to design and "tune" new and existing programs of research and training.

In addition, I must mention the discovery of the BRCA1 breast cancer susceptibility gene several months ago by researchers at the NIEHS. This work, done cooperatively with university researchers, has opened the door to the development of a test for the gene which is implicated in early onset breast cancer in a large number of women.

CLINICAL TRIALS

Mr. Stokes: Clinical Trials appear to be the backbone for bridging basic research and advances in medical treatments. NIH Clinical Trials have yielded significant health benefits to the American people and have yielded comparable economic savings as well. What level of funding is included in your Institute's FY 1996 budget for clinical trials?

Dr. Olden: The NIEHS FY 1996 budget includes just under $3 million for clinical trials. Another $2.9 million is estimated to be provided from the Office of Research on Minority Health.

Mr. Stokes: How many trials would be funded and how many of these trials are new and how many are ongoing?

Dr. Olden: There is one clinical trial, the Treatment of Lead exposed Children (TLC) trial, mentioned previously, and it is on-going.

Mr. Stokes: Is there a specific system in place at your Institute for disseminating important information resulting from clinical trials?

Dr. Olden: Yes, NIEHS uses a system, MedLine, which is coordinated through the National Library of Medicine and is available to all Institute Directors. A good recent example of its use was Dr. L'Enfant's early release of trial data showing the benefit of hydroxyurea in the management and prevention of painful sickle cell crises.

Mr. Stokes: What progress is being made in increasing the numbers of women and minorities in clinical trials?

Dr. Olden: We have only one formal clinical trial, the Treatment of Lead-exposed Children Trial. It is primarily a study of minority children; mostly African-American, some Latino. We expect that it will enroll approximately equal numbers of boys and girls.

FTEs

Mr. Stokes: Is the Institute currently under a FTE freeze, and if so, how long has it been under this freeze and how is it impacting operations?

Dr. Olden: The Institute is not currently under a freeze. The NIH had been under a PHS-agency wide hiring freeze limiting hires to personnel within the Public Health Service since December 1993. The freeze was lifted in February 1995.

NIEHS is projecting FY 1995 FTE usage to be approximately 50 below ceiling. While we have been reassigning personnel from other areas to meet the highest priority needs, many programs are seriously understaffed producing inefficiencies and lost opportunities. Of particular concern has been our inability to fully implement the clinical program and to pursue leads in breast cancer and risk assessment. Certain support activities such as animal care and breeding and laboratory renovations here had to be contracted out at a cost greater than would have been required if done with federal employees.

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GENE REPOSITORY

Mr. Stokes: What is the association between genetic predisposition and the research under the purview of your Institute?

Dr. Olden: The impact of all or almost all environmental agents is determined by the combination of the exposure and of individual susceptibilities. Susceptibility in turn is determined by a mixture of age and gender, previous history of exposure to many environmental agents, and genetic predisposition. An understanding of genetic predisposition is important in virtually all NIEHS research.

CLINICAL TRIALS

Mr. Stokes: What are some of the most significant clinical trials that are underway at your Institute? Overall, how much is included in the FY 1997 budget for clinical trials, and how does this compare to the funding levels for FY 1996, FY 1995, and FY 1994?

Dr. Olden: NIEHS is currently conducting only one clinical trial, the Treatment of Lead-exposed Children Trial. It is designed to determine whether an oral drug that lowers blood lead levels will prevent the delays in cognitive development, slowed growth, and behavior disorders caused by lead poisoning in young children. The budgets for this trial in FYs 94-97 are $6.4, 6.4, 5.2, and 5.7 million, with about half of the funding coming to us from the Office of Research on Minority Health. The budget also includes funding of $250 thousand each year in FY 1996 and FY 1997 for a pilot study on the primary prevention of asthma in children.

CLOSING THE GAP IN MINORITY HEALTH

Mr. Stokes: What progress do you have to report this year with respect to activities underway at your Institute that are designed to address the gap in minority health? Also, provide a more detailed response for the record, be as specific as possible.

Dr. Olden: The NIEHS strongly supports research aimed at achieving environmental equity for all populations. Assays of the health effects of environmental pollution, as well as regulations based on such assays, are often performed with little or no input from the affected community. The NIEHS is able to bridge this crucial communication gap through its ***Environmental Justice: Partnerships for Communication*** grant program. The main objective of this program is to establish a new research paradigm linking members of the community, who are directly affected by adverse environmental conditions, with researchers and health care providers. Seven awards span a spectrum of affected populations including Asian/Pacific Islander, African-American, Hispanic, and Native American communities. This effort has successfully heightened the awareness of the role of biomedical research and defined a new standard for outreach to minority communities by environmental health science centers and researchers.

Prostate Cancer Metastasis Gene: For men, prostate cancer is arguably their greatest cancer fear. Not only does it account for one in every four cancers diagnosed in American men, but it can spread (metastasize) beyond the prostate, killing 40,000 men annually. Although only 25% of these cancers are the lethal variety, physicians have no way of determining which prostate cancers can be ignored and which must be surgically removed. This dilemma is further complicated by the fact that prostate cancer surgery is a difficult surgery, requiring a lengthy recovery time and frequently rendering a man incontinent or impotent. A biological marker that identifies which patients are truly at risk of the cancer spreading beyond the prostate, and thus meriting surgery, would prevent unnecessary surgeries among men with non-metastatic prostate cancers. NIEHS intramural researchers, working with colleagues at John Hopkins University, have isolated the first such marker. This gene, KAI1, was shown to suppress the spread of prostate cancers in experimental animals and it appears to be lost in metastatic human prostate cancers. Its discovery will initially lead to better identification of patients requiring prostate cancer surgery. Its identification also enhances our ability to develop therapeutic strategies to more effectively treat this devastating disease. Ultimately, studies on this gene will help us identify the environmental components leading to prostate cancer development, thus enabling us to help completely prevent its development in the first place.

Lead Exposure, Its Link to Criminal Behavior, and Its Treatment: Adult criminality, alcoholism, and domestic abuse are on the rise. Our Nation's citizens are concerned for their safety and demanding these problems be remedied. Interestingly NIEHS' long history of research is revealing an unanticipated environmental component to these social problems - lead. NIEHS-supported researchers have shown that the developing fetus and young child are particularly susceptible to lead and that their brain is the most vulnerable target. Further research, published in 1990, revealed that even at exposures previously thought to be safe, young children suffer from measurable decreases in IQ scores and exhibit anti-social and delinquent behavior. A new study on a cohort of young boys in Pittsburgh's inner city confirms that above-normal lead levels are associated with more aggressive and delinquent behavior, such as bullying, vandalism, theft, fighting, and setting fires. These behaviors foreshadow the development of more serious problems as these boys become adults, including adult criminality, alcoholism, and domestic abuse. It is notable that inner city environments, which are known to have high crime rates, also suffer from high levels of environmental lead. These studies suggest a need for enhanced lead prevention programs as part of a strategy to improve public safety.

Other important research explores ways to prevent lead being absorbed and to intervene or reverse neurobehavioral consequences once this exposure has occurred. One study supported by the NIEHS and the NIH Office of Research on Minority Health is examining the ability of a chelating drug, succimer, to prevent or reverse the neurobehavioral effects of low blood lead levels in young children. Other researchers are determining how much of a child's lead burden is determined by its most important environment - its mother. Lead stored in a woman's bones can be mobilized during pregnancy and lactation, then transferred to the fetus or suckling child. This early lead exposure might be one of the most significant lead sources for children, suggesting that early testing and treatment of pregnant women is an important component of reducing lead exposure in children. Results from these ongoing studies will provide vital information in