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NIEHS

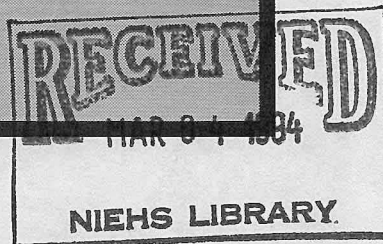
VISION FOR THE FUTURE

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MISSION STATEMENT

Human health and human disease result from three interactive elements: environmental exposures, individual susceptibility, and time. The mission of the National Institute of Environmental Health Sciences (NIEHS) is to reduce the burden of human illness and dysfunction from environmental exposures by understanding each of these elements and how they interrelate. NIEHS achieves its mission through multidisciplinary biomedical research programs, prevention and intervention efforts, and communication strategies that encompass training, education, technology transfer, and community outreach.

Visions for the Future

NIEHS scientists, university-based grantees, and senior management have forged a new vision of what NIEHS is and what its future opportunities are. Their ideas are outlined in the document *Vision for the Future* which is included in this edition of the *Environmental Factor*.

Vision for the Future revolves around two core concepts that emerged during deliberations leading to this document. The first concept is that human health and human disease can be explained in terms of three interactive elements - individual genetic susceptibility, environment, and time or age. NIEHS research focuses on understanding each of these elements and how they interrelate. The second concept defines the NIEHS in terms of its responsibilities to the Public Health Service. The fundamental concept is that NIEHS research reduces the burden of environmentally-associated disorders by providing the science base needed for good public health policy decisions, by translating this science into prevention strategies, and by communicating this knowledge to both scientific and lay communities.

The roots of this document can be traced to two events that occurred in the summer of 1991. The first event was the formation of an extramural panel to develop a Task Force Report, the fourth in an ongoing series of reports that recommend research directions and opportunities to the NIEHS. The second event was the NIH Strategic Plan in which NIEHS scientists provided 170 research proposals. These proposals were eventually incorporated into the "Basic Biology Related to the Environment" section of the NIH Strategic Plan and also provided important background material for

formulating the NIEHS *Vision for the Future*.

Dr. Ken Olden, the Director of NIEHS, says that *Vision for the Future* "provides a cohesive statement of how the NIEHS views itself and how it foresees its future. I will be using this document to structure ongoing dialogues both within and outside of the NIEHS. These dialogues will help us refine the ideas and concepts set forth in this document." Dr. Olden goes on to say that, "This document is seen as one that will continually evolve. As environmental health research moves forward, new opportunities will arise. It is important that we stay alert and receptive to these opportunities. For this reason I encourage everyone to read the document and to give us their comments and ideas." NIEHS employees can send their ideas to the Office of Program Planning and Evaluation, MD B2 08.

The two core concepts in the document have been fashioned into two triangular graphics which are shown on the next page. These graphics can be helpful to NIEHS employees in their public presentations to outside groups. The NIEHS photography contractor has these graphics on file and they can be obtained as slides or overhead transparencies.

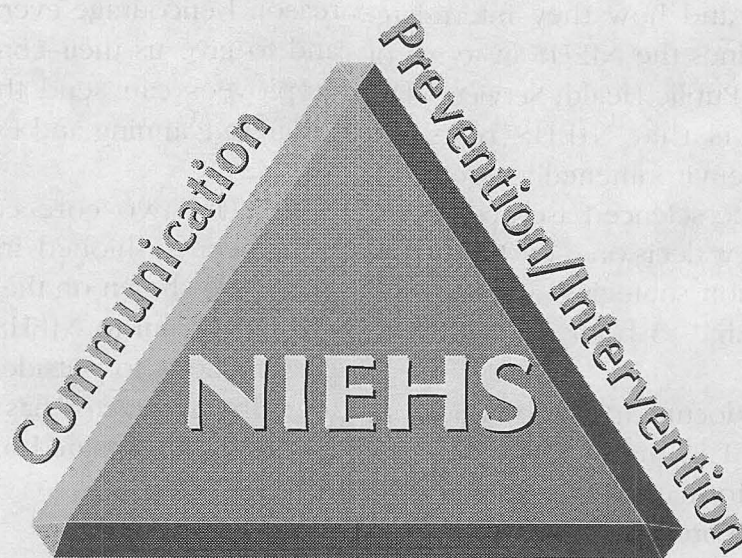


Environmental
Exposures

Intrinsic
Genetic
Susceptibility

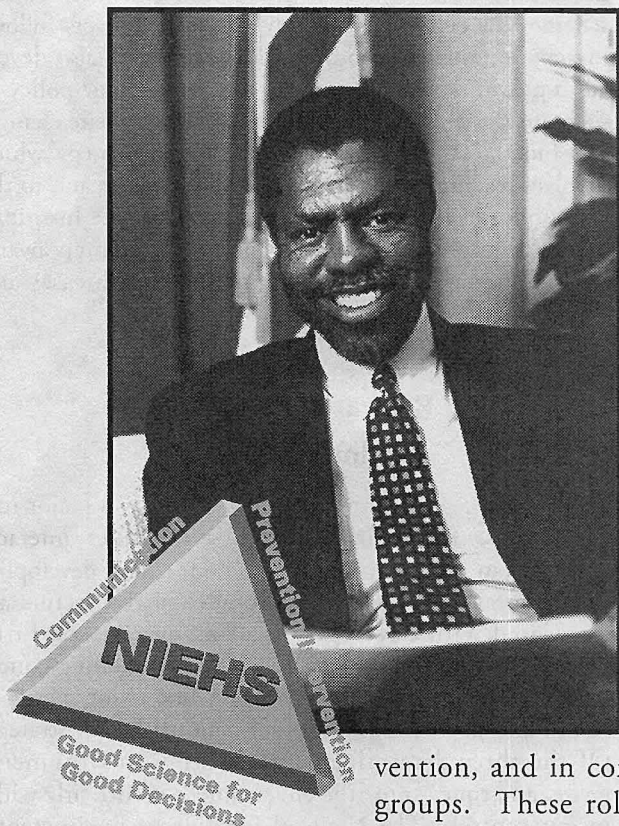
Human
Health/Disease

Age/Time



Good Science for
Good Decisions

When I was appointed Director of the National Institute of Environmental Health Sciences (NIEHS) in 1991, I immediately began to discuss with the Institute's many stakeholders their perceptions of the mission and role of the NIEHS. In addition to the more obvious stakeholders – intramural scientists, extramural researchers, and federal regulators – I had dialogues with representatives of the Society of Toxicology and other professional organizations, with industry groups, with environmental advocacy groups, with labor unions, and with economically disadvantaged groups who suffer the preponderance of environmental exposures. These dialogues, along with recommendations from the National Advisory Environmental Health Sciences Council-sponsored Task Force IV report, have been used to structure a new vision for the NIEHS which advocates strong roles in basic research, in prevention and inter-



vention, and in communication with lay and scientific groups. These roles revolve around the core NIEHS responsibility of understanding how human health and

human disease are caused by the interaction of environment and individual susceptibility over time.

The vision that the Institute has created is outlined in the accompanying document. It will be used to help set priorities for NIEHS research both intramurally and extramurally. For this reason it is important that this document be used to continue our dialogue about needs in environmental health research. This is a living plan and will be modified and changed over the course of time. We encourage groups and individuals to communicate with us about any changes that could be made, or opportunities that we overlooked, so that the document can continue to evolve.

Kenneth Olden

Kenneth Olden, Ph.D.



Executive Summary

From conception to death, we are all exposed to a multitude of environmental agents. These agents include foods and nutrients, physical agents such as heat and ionizing and non-ionizing radiation, social and economic factors that affect our health and behavior, lifestyle choices and substance abuse, and synthetic and naturally occurring chemicals. The mission of the National Institute of Environmental Health Sciences (NIEHS) is to define how these environmental exposures affect our health, how individuals differ in their susceptibility to these effects, and how these susceptibilities change over time. To fulfill this mission, the Institute must provide the science that is necessary to understand the impact of the environment on human health, must translate this information into prevention and intervention strategies, and must communicate this information to the American public.

The NIEHS mission, though formidable, is extremely important. Diseases and dysfunctions with an environmental component include cancer, birth defects, infertility, neurological impairments, immune disorders, and lung dysfunctions. Because environmental exposures can be controlled or avoided, they represent one of the most promising means of improving our Nation's health. The NIEHS will have an increasingly important role to play in the future as public policy makers struggle to balance human health needs with the economic benefits of commercial processes that might endanger that health. Their decisions will only be as good as the scientific foundation upon which they rest.

Environmental health research is at a critical and exciting juncture. New refinements in molecular biology techniques provide unprecedented opportunities to understand the molecular and cellular basis of environmentally-associated diseases. These research opportunities, however, must be balanced against the constraints of a limited budget. In order to ensure that its resources are spent on the most promising research areas, the NIEHS recently underwent an extensive planning exercise. Both the intramural and extramural communities were involved, and consensus among the Institute's many research partners is being sought. Areas for concentration of NIEHS efforts were selected based on their ability to meet three criteria: (1) they had to address an area that was ripe for exploration; (2) they had to represent a significant public health problem; and (3) they had to be an area for which the NIEHS' intramural or extramural communities had genuine research strength. The research priorities were structured around the core NIEHS responsibilities of providing the good science needed for good public health decisions, of translating this research into prevention and intervention strategies, and of communicating this information to the scientific and lay communities.

The accompanying document outlines the NIEHS vision for fulfilling its mission. Highlights of this document include the need to focus on environmental components of human disease, the need to understand the basic biology of environmentally associated disorders, and the need to use this mechanistic understanding of environmentally caused effects in risk assessment schemes. This fundamental knowledge opens new opportunities for developing novel molecular prevention and intervention schemes for circumventing adverse health effects following environmental exposures. The NIEHS is also devoted to providing the science base needed to guide policy in such areas as environmental equity, global climate change, and bioethics. Finally, a communication strategy which involves reaching out both to research partners and to the lay public, is envisioned as a cornerstone of the Institute's efforts to improve our Nation's health through an awareness of the environmental components of diseases and dysfunctions.

Research Priorities

I. Introduction

A. Overview: Environmental exposures play a major role in our lives. Over our lifespan these exposures, interacting with our genetic makeup, affect our risk of developing a wide array of diseases. Environmental risk factors are associated with development of many cancers, birth defects, breathing disorders, and other debilitating conditions. Understanding the environmental components of health and disease is pivotal to a national health strategy. Of the three determinants of health – environment, genes, and time – only the environment is currently within our control. The National Institute of Environmental Health Sciences was created to address this critical research area.

The mission of the (NIEHS) is to define how environmental exposures affect our health, how individuals differ in their susceptibility to these effects, and how these susceptibilities change with time. To help reduce the burden of environmentally associated diseases, the Institute must provide the science that is necessary for understanding the impact of the environment on human health, translate this information into prevention and intervention strategies, and communicate this information to the American public.

B. Historical Perspective: The NIEHS is located in the Research Triangle Park, North Carolina. Since its creation in 1966, the Institute has been the primary source of federal efforts for studying how environmental factors affect human health. Because of the broad scope of its mission, NIEHS research relies on essentially every discipline in the biological, chemical, and physical sciences.

It maintains a multidisciplinary intramural research program at its Research Triangle Park facility, manages a large testing program for the National Toxicology Program (NTP), and supports university-based research and training through a variety of grant mechanisms.

NIEHS-supported research has provided some of the most significant research findings in the environmental health sciences. Examples include:

- *Lead Exposures* – NIEHS-supported studies showed that even low-to-moderate lead exposures can cause learning disabilities and behavioral problems in children. These results galvanized the public health service, Congress, and communities to strengthen programs to reduce lead in the environment.

- *Dioxin Health Risks* – Dioxin, a manufacturing by-product that is widely distributed in the environment, is known to cause cancer, reproductive impairment, and other toxic effects. What is less certain, however, is the relative potency of its effect in people. NIEHS scientists provided the quantitative and qualitative information that was pivotal in EPA's determination of allowable dioxin levels that would protect the public health. This work also illustrated the power of mechanistically-based data in developing relevant regulatory standards.

- *Testing Program* – Through its participation in the National Toxicology Program, NIEHS has made significant contributions in providing state-of-the-art toxicological characterization for a host of commercially important environmental agents. Because of the irrefutably high quality of these studies, they serve to guide risk assessments both in this country and abroad. Additionally they are an outstanding resource for evaluating the usefulness of short-term assays and mathematical prediction schemes.

- *Basic Research* – Studies at NIEHS have provided important insights into the basic mechanisms of chemical toxicities, including mutagenesis and the role of oncogenes and tumor suppressor genes in chemical carcinogenesis. Another area of emphasis has been the action of exogenous estrogens, especially as they affect development and hormonal carcinogenesis. NIEHS-supported studies on the mechanics of such processes as cellular signalling, cellular differentiation, and cellular aging enable us to better understand the actual mechanism by which environmental agents can cause disease.

C. Oversight and Review: The NIEHS supports work through three funding mechanisms: intramural research, grants, and contracts. The mechanisms are chosen based on whether the work could be best done intramurally, by extramural scientists via grants, or by the private sector via contracts. Each of these mechanisms has a separate review process.

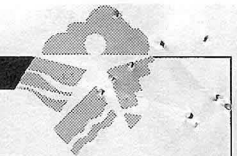
Work in intramural research laboratories is reviewed every four years by an external group of experts, the NIEHS Board of Scientific Counselors. The Board evaluates both the relevance of the research pursued and the quality of the research done. Management recommendations, such as increasing support in a particular area or terminating support of some research, are made to the NIEHS Director and to the Scientific Director who are responsible for responding to all Board recommendations.

Grants are competitively awarded every three to four years. Special study sections composed of non-federal research scientists evaluate and rank all grants received within a funding cycle. The highest ranked grants are awarded based on the NIEHS budget and the National Advisory Environmental Health Sciences Council's (NAEHSC) concurrence. The NAEHSC is the Institute's final review board and is composed of external specialists in environmental health science, economics, and management. This group also advises the NIEHS about the need to dedicate special funds to areas of environmental health that represent important underfunded research needs.

Contracts are awarded competitively and are generally for one to five year periods. All intramural contracts must be evaluated by an internal committee of upper management scientists to ensure that the most relevant research efforts are supported. Contracts awarded for studies in support of the National Toxicology Program must go through additional approval from the NTP Board of Scientific Counselors, consisting of non-federal scientists, and the NTP Executive Committee, composed of the agency heads of the NTP components.

D. Future Plans: We live in a world of change. The biomedical research community, in particular, has seen tremendous change over the last decades. New refinements in molecular biology techniques provide exciting opportunities for understanding the molecular and cellular basis of disease. Unfortunately these opportunities are coupled to a changing fiscal situation. The research possibilities that excite us must be balanced against the constraints of a limited budget.

These limitations have special significance for NIEHS. Research needs in environmental health science are increasing at a time when financial resources are not. New chemicals and technologies are constantly coming on the market. Even established technologies, such as the generation and transmission of electricity, are being questioned for their subtle impacts on human health. In response to these changes, the NIEHS embarked on a planning exercise to define the most promising areas of research upon which to focus its support and efforts.



Two planning exercises were conducted, one external and one internal. The external planning exercise, managed by the National Advisory Environmental Health Sciences Council, culminated in the fourth of a series of Task Force reports¹ to help guide NIEHS research. The internal planning exercise involved solicitation of ideas from the entire research community within NIEHS to help define the directions they thought NIEHS should take. This document synthesizes the two planning exercises. It provides a brief description and rationale for the most promising areas of research that were identified in the two planning exercises. Those readers who wish greater scientific detail are referred to the Task Force IV Report¹.

Priority areas selected for this document had to meet three criteria: (1) they had to address an area that was ripe for exploration and where a positive outcome could be expected over the next five years; (2) they had to represent a significant public health problem; and (3) they had to be an area for which the NIEHS' intramural or extramural communities had genuine research strength. Discussion of these priority areas is organized around the three core NIEHS activities - providing the science base for public policy decisions, using this information for prevention and intervention purposes, and communicating environmental health information and concerns among the Institute's multiple constituencies.

E. Uncertainties: This document represents the Institute's best effort to articulate the most promising areas of environmental health research. These priorities, however, are necessarily flexible and will change as circumstances change. These circumstances might come in the form of new technological innovations, new data, changed budget lines, or Congressional mandates. For these reasons the Institute expects to revisit and update its priorities periodically.

II. Good Science for Good Decisions

Environmental health policy is only as good as the scientific foundation upon which it rests. NIEHS' challenge is to maximize the effectiveness of public policy decisions by providing the most complete information on the environmental components of human disease and on the biological mechanisms by which these diseases occur.

A. Environmental Components of Human Disease: Although an environmental component for a number of human diseases and dysfunctions can be logically presumed, identifying actual causative or promoting agents has proven difficult. For those disorders with suspected environmental components, increased research efforts are needed to identify these agents and the mechanisms by which they act. Of particular interest to the NIEHS are environmental components of women's, children's, and

minorities' health, aging, lung diseases, neurological and immune system dysfunction, and cancer. Additionally, the Institute is interested in promoting clinical research programs that can more readily translate laboratory-based findings into practical human therapies. These topics are listed below in more detail; the order in which they appear does not indicate a priority ranking.

- **Women's 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. Women are more likely than men to develop autoimmune diseases such as multiple sclerosis and systemic lupus erythematosus; environmental factors are thought to play a role in these diseases. A number of wide-spread environmental toxicants (e.g., DDT, polychlorinated biphenyls) 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. The Institute's long-standing commitment to research on environmental components of women's health will continue; the above research represents areas of special emphasis.

- **Children's Health** – 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. This work is particularly compelling because in 60% of birth defects the causes are unknown. An environmental component is suspected for many of these birth defects, and further study is obviously merited.

- **Minority Health** – African-American, Hispanic, and Native American populations have a poorer health status, overall, than do Caucasian-Americans. This disparity might in part arise from the fact that minority populations are more likely to be exposed to environmental toxins such as lead and other metals, agricultural chemicals, and petrochemicals. For these reasons the NIEHS has long supported research into the health effects of environmental and occupational compounds to which minority populations are exposed. This research emphasis will continue and health risk data will be examined to determine other fruitful lines of investigation.

- **Aging** – The incidence, prevalence, and severity of many chronic conditions increase with age. As this segment of the U.S. population increases, it will be important to understand which conditions are an inevitable

¹ *Human Health and the Environment - Some Research Needs*, Department of Health and Human Services, 1992. Pub. No. 92-3344

consequence of aging and which are due to cumulative effects of low-dose environmental exposures that could be prevented. Furthermore, we need to understand how environmental exposures can affect the progression of existing disease states such as cardiovascular impairments, decreased immune responses, and other deficits.

- *Respiratory Disorders* - Inhaled pollutants enter the body through the respiratory system. The vulnerability of this system is aptly demonstrated by the many lung diseases caused by inhaled particles (e.g., asbestosis and brown lung disease) and the increased hospitalizations for respiratory distress observed in areas with poor air quality. The Institute will continue supporting research into environmental causes of respiratory disorders. Additionally it will increase support into understanding the environmental triggers of asthma, a lung condition for which mortality rates increased 40% in the U.S. during the 1980s.

- *Neurological and Neurobehavioral Disorders* - A wide range of environmental compounds affect the nervous system. The list of known neurotoxins includes many pesticides, solvents and metals. Although neurotoxic effects at high concentrations are a concern, research also must examine the subtle effects of low-dose exposures. The validity of this concern has been aptly demonstrated by research into lead toxicity where even relatively low blood lead levels in children were later associated with reduced intelligence scores and lowered chances of graduating from high school. Another research need is to define neurotoxic effects that have long latency periods between exposure and clinical expression of disease. Neurodegenerative diseases such as Alzheimer's, Parkinson's and amyotrophic lateral sclerosis might fall into this class. Understanding the basic mechanism of neurotoxicity and relating neurotoxic events to neurobehavioral outcomes and clinical disease represent important areas of continued research interest for the NIEHS.

- *Immune System Disruption* - The immune system directs the body's response to invasions by foreign substances. Obviously exposures to the plethora of chemicals in our environment would have an impact on immune system function. Environmental exposures could affect human health by disruption of immune system function in three distinct ways. One way would be by direct toxic action to cellular components of the immune system, resulting in an immunocompromised individual. Another possibility would be the attachment of an environmental agent to endogenous host material in a way that would confer autoimmunity. Several autoimmune diseases, including multiple sclerosis and systemic lupus erythematosus, might develop in this way. A third effect would be an enhanced sensitivity of the immune system to a particular environmental antigen, leading to heightened immune system responses to all subsequent exposures. Understanding the environmental components of

immune system dysfunction is clearly important. This research area is increasingly amenable to study following recent advances in monoclonal antibody technology, cell sorting techniques, and development of animal models such as the severe combined immunodeficient (SCID) mouse.

- *Cancer* - An environmental component for many cancers is clearly established. Since its inception, the NIEHS has supported work exploring the connection between environmental exposures and cancer risks. The Institute will continue examining the link between the environment and cancer development through research into the etiology of cancer and the mechanisms of environmental carcinogens.

- *Human Studies and Clinical Research* - Environmental health research has been hampered by a paucity of clinical facilities devoted to environmentally-related diseases and disorders. In order to improve its ability to translate basic research findings into practical treatments for people, 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 clinical research and expertise at these centers 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.

B. Basic Biology of Environmental Disorders: To date a large part of environmental health research has focused on identifying the environmental causes of diseases. Future research promise lies in understanding the actual molecular and genetic basis of environmentally-caused disorders. Recent advances in molecular biological techniques will enable environmental research scientists to develop more detailed and meaningful understandings of the interaction of environmental agents on basic cellular functions. This knowledge in turn can be used to develop molecular prevention and intervention schemes, to promote more mechanistically-based risk assessment, to identify useful molecular indicators of environmental exposure and effect (i.e., "biomarkers"), and to develop structure-based design schemes for pharmaceuticals and pesticides. Areas which the Institute is particularly interested in supporting include environmental effects on cell proliferation and apoptosis, events controlling differentiation and development, receptor-mediated pathobiology, and genetic susceptibility and predisposition to environmentally-associated diseases.

- *Target Genes for Environmentally-Induced Effects* - Genes control cellular differentiation, division, and death. Good health depends on the proper functioning of these genetic controls. When critical genetic material is altered,



the functions over which it exerts control can go awry, leading to birth defects, cancer, neurobehavioral abnormalities, and other diseases and dysfunctions. A better understanding is needed of the individual roles of these genes, the ability of environmental agents to interact with and damage them, the relationship between a xenobiotic's chemical structure and its binding affinity to critical cellular targets, and the consequences of genetic malfunction. Among the genes meriting further study and characterization are those responsible for programmed cell death, regulatory genes which direct embryogenesis, DNA repair genes, mitochondrial genes, "heat-shock" genes, oncogenes, and tumor suppressor genes.

- *Cellular Communication Pathways* – Human health depends on a complex network of chemical signals between cells. The molecules that transmit these signals are primary targets of toxic substances in the environment. Identification of the role of individual protein messengers and receptors in cellular determination, growth, differentiation, and 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. Particularly fruitful lines of inquiry include the effect of environmental factors on signal transduction pathways and the ability of environmental agents to bind to critical protein receptors such as the estrogen receptor, Ah receptor, excitotoxin receptors, oral and nasal chemoreceptors, and "orphan receptors."

- *Integration Across Organ Systems* – Organ systems do not operate in isolation. Communication pathways exist between them and need to be defined. This understanding is particularly important in the field of environmental health sciences where damage to one system can translate into toxic effects across multiple systems. Of particular interest to the NIEHS is the neuro-endocrine-immune axis. The parallel development of this system, the receptors and soluble mediators shared by its members, and the ability of environmental agents to disrupt the integration of this system are important avenues of study.

- *Individual Susceptibility* – The variation in individual responses to environmental agents is exceptionally wide. This variation is accounted for by differences in metabolic capacity (polymorphisms in drug-metabolizing or detoxifying enzymes), 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 environmen-

tal component can be presumed. By using this technology to identify particularly susceptible subgroups, scientists will be able to better identify environmental risk factors for many diseases and to understand the mechanisms leading to these diseases.

III. Prevention and Intervention

Understanding the environmental components and basic biology of disorders can lead to prevention and intervention strategies to circumvent many adverse health effects. Traditionally these strategies have focused on primary prevention techniques such as eliminating or reducing environmental exposures. These techniques will continue to be important parts of the Nation's environmental health programs. An integral part of this program is the development of the science that will enable risk assessors to determine how much reduction of exposure is needed to protect public health. Generating risk assessment levels relies strongly on rodent data and on extrapolation of results in rodents to probable effects in humans. The relevance and power of these assessment schemes will be greatly enhanced when the biological mechanisms for adverse effects are incorporated into the mathematical models used to estimate risks from low exposures.

As we understand the molecular and cellular basis of environmentally-associated diseases, secondary prevention and intervention techniques could be developed to treat people following an adverse environmental exposure. These molecular intervention techniques would rely on manipulations of the biological mechanisms underlying environmentally-induced diseases, such as activating and inactivating enzymes, receptors, and other molecular components. They would be particularly useful in dealing with environmental exposures that are ubiquitous or difficult to eliminate. Further, they would have important implications in the pharmaceutical and pesticide industries, which could in the future develop products with maximal effectiveness and minimal side effects based on a structural understanding of underlying biological mechanisms.

Prevention and intervention schemes must also take into account the social and cultural lifestyle and behavioral factors that contribute to environmentally-associated disorders. It is part of NIEHS' responsibility to provide the scientific foundation that can structure and define discussions on the contribution of societal and cultural behaviors in the development of these disorders.

Training is another part of prevention and intervention strategies. A well-trained medical workforce that is able to identify environmental components of diseases will be critical to protecting human health. Equally critical will be providing for a laboratory-based research workforce that is both multidisciplinary and multicultural. The

NIEHS has incorporated training strategies to meet all of these needs.

A. 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 utility of these techniques will be greatly improved as new insights into the molecular basis of toxic effects are incorporated into study designs.

- **Mechanistic Data** – Animal studies often provide only descriptive information, revealing the toxicity of an environmental agent by its ability to cause adverse effects such as tumors, histopathologic abnormalities, or genetic changes. An even more meaningful way to relate animal studies to human health effects is by determining the underlying mechanisms leading to toxicity. Recent developments in molecular biology can potentially lead to studies that generate more meaningful, mechanistically based data. For example it will be increasingly possible to explain tumors in terms of oncogene activation and to relate oncogenes in animals with those in humans; environmental effects in the future can be explained in terms of disruption of critical cellular components such as receptors and signalling pathways, and these in turn can be compared across species. Because of the multidisciplinary nature of NIEHS, the Institute is uniquely positioned to ensure that new insights arising from laboratory and clinical studies on the basic biology of environmental effects are incorporated into hazard identification studies.

- **Biomarkers** – Hazard identification is often handicapped by an inability to determine individual exposure levels or to account for individual differences in uptake and distribution of toxicants. As our knowledge of the molecular components of environmental exposures increases, biological indicators (biomarkers) to measure both exposures and effects can be developed for use in both epidemiologic and testing studies. Ideally these indicators would be noninvasive, sensitive, and specific to a particular exposure. Potentially biomarkers could be used in screening programs for exposed human populations to provide early warning of environmental exposure, predict development of disease, and enable clinicians to prescribe appropriate intervention therapies. International studies on highly exposed populations offer excellent opportunities for developing and validating biomarkers.

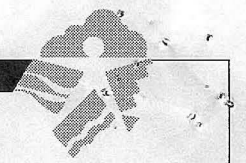
- **Non-cancer Endpoints** – Although cancer has been a major focus of past efforts in environmental health science, there needs to be a more balanced assessment of the full spectrum of possible environmentally-associated effects. Important endpoints in addition to cancer include birth defects, infertility, neurological impairments, immune system dysfunction, and respiratory distress. As we improve understanding of the molecular and cellular basis of the entire host of physiological functions, this

knowledge can be used to design studies that assess a broader range of possible health endpoints. These assessments also will be improved when attempts are made to understand toxicological effects in terms of their molecular and cellular actions across multiple organ systems rather than in single organ systems.

- **Development of Animal Model Systems** – Human and animal system models are integral to intervention studies. These models will be used to understand how an environmental agent causes a disease and to determine which particular chemical interventions are useful in interfering with disease progress. One promising example is the development of transgenic animals that duplicate human diseases. Other avenues for exploration include the development of alternative animal models to replace rodents. New developments in molecular biology offer the possibility of using nonmammalian animals for quicker assays with results comparable to the long-term rodent studies. Molecular biologists have convincingly shown that there is tremendous evolutionary conservation across species of the genetic controls governing physiological and biochemical regulatory mechanisms. For this reason fish, frogs, insects, and other nonmammalian organisms should be evaluated for use in assays to predict health effects of environmental agents. Adverse health effects for which these assays could prove useful include cancer, birth defects, infertility, immune system impairments, and neurological dysfunctions.

- **Sentinel Animals** – The above initiatives have all assumed the use of laboratory animals. One underutilized aspect of hazard identification, however, is the use of wildlife to serve as sentinels for human risks from exposures, particularly exposures to agricultural chemicals and industrial pollutants. Most recently these animals have alerted biologists to the possibility that environmental estrogens, such as DDT metabolites and polychlorinated biphenyls (PCBs), can adversely affect reproduction and sex characteristics. Other possibilities include the use of marine life to detect pollutants and the use of aquatic plants to detect early changes in water quality.

B. Risk Assessment: Hazard identification and characterization are only the first steps in prevention schemes. Risk assessors must take this information and translate it into acceptable exposure levels for people. Implicit in all risk assessment schemes is the need to extrapolate from high-exposure studies to low-exposure situations and from known risks in rodents to probable risks in people. Both extrapolations are fraught with uncertainties. These uncertainties are accommodated in risk assessment schemes by the incorporation of arbitrary "safety factors" and other default approaches such as scaling factors; since these factors are not derived experimentally, they may well over-estimate or under-estimate risks. Risk assessment methodology, its relevance to the human condition, and



its use in protecting human health will be greatly improved when our expanding knowledge of the basic biology of environmental effects is incorporated into toxicological testing and risk assessment schemes.

- *Improving Risk Assessment Models* – The mathematical manipulations used to generate risk assessment values represent an area where NIEHS scientists can make important contributions. The NIEHS has a multidisciplinary array of scientists, including biostatisticians, toxicologists, epidemiologists, and molecular biologists. Working together they can help develop improved risk assessment models for use by regulatory agencies. A particularly promising area in which the NIEHS has a role to play is in developing mechanistically relevant risk assessment schemes. Laboratory animals and humans share many common biochemical and physiological pathways. At the same time, there are important differences that might be critical in translating animal data into human risks. Data need to be generated that enable risk assessors to judge the relevance to humans of environmentally-induced changes in laboratory animals.

- *Molecular Dosimetry* – At present toxic effects in animals are detectable only at relatively high doses. Molecular changes, however, can be detected at lower doses. As our knowledge of the molecular mechanisms underlying toxic effects improves, this information can be used to strengthen our ability to extrapolate from high-dose exposures to low-dose exposures. Molecular biological techniques can be used to generate models for tissue delivery of toxicants, changes in gene expression, and tissue response differences.

- *Individual Variation in Response to Environmental Agents* – Current risk assessment schemes relate risks to the general population, not to specific subpopulations. As information emerges on the specific features that lead to enhanced susceptibility - i.e., specific genes, age-related factors, nutritional status - these factors can be used to determine risks to susceptible individuals or populations. The possibility exists that future risk-assessment levels will be calculated to protect the most vulnerable part of the population (pregnant women, children, elderly, genetically predisposed groups) rather than a hypothetical "average" human.

C. Molecular Prevention/Intervention: Human health and human disease are both outgrowths of molecular events. Understanding the basic biology of these molecular events offers considerable promise for preventing disease development. As molecular biologists gain insight into environmental components of disease, new molecular strategies can be developed that either prevent these diseases or intervene in their progression before they become debilitating. Future possibilities include:

- *Nutritional Interventions* – It is particularly important to understand the effect of nutritional status on susceptibility to environmental compounds. For example, it

has been observed that adding iron, calcium, zinc, and protein to diets will decrease uptake of lead in children and adults living in moderate-to-low lead exposure environments. The possibility that nutrient metals compete with lead and other environmental metals for regulatory receptors, channels of uptake/transport, and portals of entry merits further study.

- *Enhancement of Detoxifying Enzyme Systems* – Numerous enzymes exist, particularly in the liver, that metabolize foreign compounds in a way that often inactivates and detoxifies them. Enhancing the rate at which detoxification occurs, especially in individuals with low levels of these enzymes, could reduce the incidence of many environmentally-associated diseases. One metabolism modifier, oltipraz, is already being studied as a means of intervening in aflatoxin-induced liver cancer.

- *Receptor Blockers* – Biological functions often rely on binding of important biological molecules to protein receptors. When environmental toxicants bind to these receptors, however, the processes they control can be permanently "turned on," leading to disease or dysfunction. Specific receptor blockers offer an innovative way of intervening in receptor-mediated environmental diseases.

- *Enhancement of DNA Repair Systems* – The human body has a number of mechanisms by which environmentally damaged DNA can be repaired. Further study could lead to biochemical enhancements of these natural repair mechanisms, thus preventing clinical expression of some diseases.

D. Science Base for Social Policy: The NIEHS exists within a larger social framework. Its responsibilities to the community require that it address many of the divisive social and political issues that revolve around public concerns for a safe environment. The NIEHS' role is to provide the scientific foundation needed to structure productive public discussions of these sometimes contentious issues.

- *Environmental Equity* – Environmental equity is a newly emerging social issue. It refers to the fact that where one works and lives is a matter of choice largely dependent upon socioeconomic factors. Intuitively, one would expect that the poor and politically disenfranchised are at a greater risk of living near hazardous waste sites or working at hazardous occupations. For these reasons they would be more likely to suffer from environmentally-related diseases than would those in the middle- and upper-socioeconomic classes. It is a logical extension of the Institute's mission to explore the dimensions of the Nation's environmental equity problem.

- *Global Climate Change* – The consequences of man-made activities in terms of global warming and ozone depletion is a hotly contested environmental issue. The NIEHS' role is to provide information on health effects expected from climate change and the technologies that

arise to circumvent these changes. Research possibilities include: expected health effects of increased UV light exposures; the toxicologic characteristics of proposed replacements for ozone-depleting chloro-fluorocarbons (CFCs); health effects of fuel oxygenators, new metals used in solar cells and batteries, and air pollution.

- *Bioethics* – Our ability to identify at-risk individuals could potentially be misused. At-risk individuals could be denied employment, health insurance coverage, or life insurance policies. The social and ethical problems surrounding use of biomarkers and genetic susceptibility information need to be anticipated and rational schemes devised to circumvent the misuse of this technology.

E. Professional Education and Training: Ensuring that our Nation has an adequately trained workforce for its future needs has been a primary responsibility for the NIEHS. These efforts are aimed at guiding the development of the multiple disciplines needed to address environmental health problems, at ensuring the future workforce adequately represents the diversity of the U.S. populations, and at developing training programs for health care providers.

- *Multidisciplinary Workforce* – Success in environmental health sciences draws upon virtually every discipline in the biological and physical sciences. Additionally the increased need for mathematical modeling and structure-based risk assessment schemes have increased the need for individuals trained in computer technology, mathematics, and biostatistics. The Institute is particularly anxious to train individuals in cross-discipline specialties such as nutritional toxicology, molecular epidemiology, biophysical chemistry, and neuro-endocrine-immuno toxicology.

- *Multicultural Workforce* – The U.S. enjoys a highly diverse population. This diversity, however, has not always been revealed in the composition of the scientific workforce or in the types of projects funded by biomedical research organizations. The NIEHS serves to encourage full representation of minorities and women by including research projects that focus on minority and women's health issues, by training a cadre of future scientists that reflects the ethnic and gender composition of the U.S. population, and by ensuring that these populations are not hindered in competing for NIEHS grants and contracts.

- *Professional Education* – Laboratory-based research is only one of many possible applications of environmental health training. Health care providers, particularly physicians and nurses, need to be able to identify environmental components contributing to disease and dysfunction. The NIEHS is supporting curricula development on the environmental basis of health problems for inclusion in medical school classes for physicians and nurses.

IV. Communication

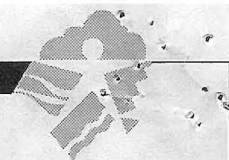
The usefulness of NIEHS research findings can only be realized when these findings are shared with public policy makers, other governmental agencies, health professionals, and the American public. Recognizing this need, the NIEHS is developing outreach programs for its many constituencies and hopes to develop improved partnerships with regulatory and research agencies, environmental advocacy groups, labor unions, and industry. These communication efforts flow both ways. Not only does the NIEHS wish to keep others informed of its research findings, but the Institute also wants to ensure that its research portfolio addresses the needs of the many public groups it serves.

A. Public Education: The major focus of NIEHS training efforts is on professional training (see above). It is obvious, though, that a nation as technologically advanced as the U.S. needs an informed and scientifically literate lay public. To help develop this level of literacy in our future leaders and voters, the NIEHS has embarked on a pilot project to explore innovative ways to educate students in grades K-12. The basic concept is to use environmental issues to illustrate to students the application of biological and chemical principles on events that touch their daily lives. It is hoped that this program can be used both to educate and to excite students about science and its environmental applications.

Understanding the health consequences of environmental exposures can also empower workers and the public to identify and to avoid hazardous environmental exposures. The Worker Safety Training Program that was developed and implemented by NIEHS in response to congressional mandates arising from the Comprehensive Environmental Response, Compensation and Liability Act (Superfund) serves as a model for using worker education to reduce risks of environmentally- and occupationally-related diseases.

B. Partnerships - Interagency: There are many federal agencies responsible for different aspects of environmental health. Unfortunately there are few formal organizational structures to ensure communication and collaboration among them. For this reason the NIEHS recently instituted a formal summit, to meet every six months, at which the directors of federal organizations with a stake in environmental health research can meet to exchange information and ideas. The organizations represented are the NIEHS, the Environmental Protection Agency, the Food and Drug Administration, the Centers for Disease Control and Prevention, the Department of Energy, and the Department of Defense.

C. Partnerships - Non-federal: There are a vast number of private advocacy groups who have an interest in the results of toxicological studies generated by the



NIEHS/NTP. These groups include environmental advocacy groups, labor unions, industrial consortia, and animal welfare groups. The NIEHS is developing ongoing dialogues with these organizations in the hope that the unique expertise and perspectives of these groups can help lead to improvements in the design of toxicological studies. The NIEHS/NTP is considering methods by which partnership outreach can become an integral part of the institutional process.

D. Partnerships - International: Environmental health problems are neither local in scope nor short-term in nature. Local activities can have global impacts which may not be easily reversible or amenable to quick technological fixes. Assessing the complex environmental health problems facing today's society requires international cooperation on an unprecedented scale. The NIEHS needs to continue to take a leading role in conducting international collaborative research and information exchange efforts in environmental health. International collaboration ranges from informal, direct contact between investigators to formal, collaborative research under country-to-country agreements, efforts involving multinational organizations, research grants and training programs, fellowships, and international meetings, symposia, and workshops. The ability to draw upon international communities, both as study populations and as collaborators, will greatly enhance the NIEHS' efforts outlined in the previous sections of this document, particularly in defining environmental components of human disease, developing a mechanistic understanding of environmental disorders, and identifying and validating biomarkers of environmental exposures and effects. Areas holding the greatest promise include the following:

- **Exposed Populations** – The world's populations offer numerous unintentional experiments in which accidental exposures to high levels of specific contaminants have occurred. Studies in these populations could be used to (1) define the human health risks of specific exposures; (2) identify reliable molecular markers ("biomarkers") of environmental exposures and effects; and (3) evaluate the effectiveness of pharmaceuticals and remediation schemes in treating exposed populations.

- **Uniformity** – Currently laboratory studies are conducted and evaluated in ways that can vary from country to country. This diversity restricts the ability of U.S. scientists and regulators to use this information in risk assessments. The NIEHS can play an important role in helping the international community develop unified study designs, protocols, and histopathologic interpretations which could enhance the transfer of knowledge generated by different international laboratories.

- **Information Exchange** – The NIEHS needs to continue sponsoring collaborative workshops, symposia, and research projects to enhance the exchange of knowledge

and perspectives among scientists in different geographical and cultural settings.

E. Community Outreach: Environmental concerns tend to be localized. Farming communities in Iowa have different concerns than fishing communities in Maine. In order to extend its presence throughout the Nation and to offer specialized services to such diverse populations, the NIEHS has called upon its Environmental Health Centers to develop community outreach programs. Community outreach is now considered a critical component of the Centers' performance and has been included as a measure of Center success.

F. Technology Transfer: NIEHS-supported research has potential for many practical applications. Innovative assay systems and predictive schemes are of obvious use to the toxicology community. Molecular understanding of environmental health effects should lead to a host of useful therapies, including tests which can identify people susceptible to adverse drug reactions, drugs to treat disorders induced by environmental agents, and practical means of circumventing damage from environmental exposures. NIEHS encourages its grantees and intramural scientists to consider the practical applications of their research and to expedite technology transfer. It also participates in the Small Business Innovative Research Program (SBIR) as a more formal means to achieve this goal.

G. Environmental Health Perspectives: No scientific journal at present definitively addresses environmental health issues. Consequently the Institute has redesigned its journal, *Environmental Health Perspectives (EHP)*. In the future the journal will be published monthly and will contain three important sections. A news section will report important and controversial issues surrounding environmental health, including regulatory actions, innovative technological and conceptual research advances, and information on fellowships and grants. This section will be aimed at both the scientific and informed lay public. Another section will contain perspectives and commentary and will serve as a forum for discussion, opinion, and the circulation of ideas. The majority of the journal will contain high quality, original, peer-reviewed, scientific articles. All aspects of environmental health will be considered, ranging from the most basic molecular biology through medicine, toxicology, physiology, epidemiology, risk assessment, hydrology, engineering, and atmospheric physics. The Institute will continue to publish, as a monograph series, important conferences and symposia on environmental health topics.

H. Workshops and Symposia: NIEHS workshops and symposia will continue to be used to identify important, emerging research issues, to focus scientific discussion on these issues, and to develop consensus on research needs and approaches.

V. Summary

Our health is determined by both intrinsic genetic factors and extrinsic environmental factors. How these factors interrelate varies over time. Of the three factors – environment, genetics, and time – only environmental factors are reasonably within our control. For this reason it is critical that we arrive at a better understanding of the environmental components of health and disease. This knowledge will lead to an improved ability to complete our natural lifespans in a way that ensures health and independence.

The NIEHS mission is to understand how environment, genes, and time interact to affect our health. Environmental health research supported by the Institute provides the solid scientific foundation to understand these interactions and, when communicated to the lay and scientific communities, can lead to effective prevention and intervention schemes. Within these three areas – basic science, prevention/intervention and communication – the NIEHS has attempted to identify the most promising strategies to fulfill its mission. These strategies are necessarily fluid and priorities will change as technology and understanding change.

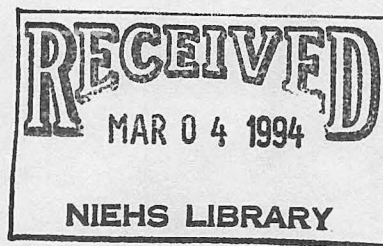
Basic science supported by the NIEHS attempts to identify the environmental components of human disease and to understand the basic molecular mechanisms leading to these disease states. Environmentally related diseases of special interest to the Institute are those dealing with women's health, children's health, minorities' health, aging, respiratory disorders, neurological and neurobehavioral disorders, immune system disruption, and cancer. Cellular processes that hold promise for explaining environmental mechanisms for the above diseases include regulatory genes that serve as targets for environmentally-induced effects, cellular communication pathways, the integration of biological processes across organ systems, and the genetic basis of individual susceptibility to environmental agents and the diseases and disorders they cause. The NIEHS also is expanding its clinical research

programs to enable it to more readily translate laboratory-based findings into human therapies.

Prevention and intervention efforts are a major focus of NIEHS activities. These efforts include hazard identification and characterization, both through traditional animal testing and epidemiologic studies and through incorporation of mechanistic considerations to arrive at new insights into the molecular basis of toxic effects. This improved understanding of the molecular foundation of environmentally-associated effects will enable the Institute to strengthen the validity of risk assessment schemes as a means of deciding regulatory policy. An improved understanding of the molecular basis of toxicant action could also lead to innovative molecular prevention and intervention therapies to circumvent clinical manifestations of environmentally-caused diseases. Prevention activities of NIEHS also focus on providing a science base for social policies such as environmental equity, global climate change, and bioethics. Training the workforce necessary to meet these challenges is another responsibility of the NIEHS and will be managed in a way that ensures both the multidisciplinary and multicultural composition needed to address future environmental health problems.

The NIEHS has also devised a communication strategy which ensures that the basic and applied research it generates reaches the groups that need it. These groups include the lay public and the Institute's partners in research, governmental agencies, advocacy groups, and the international community.

By focusing on the initiatives outlined in this document, the NIEHS will provide the information needed to implement public health policy that reduces the burden of human illness and dysfunction from environmental causes. This information, effectively communicated, will enable individuals to make intelligent lifestyle choices, will enable risk assessors to arrive at exposure levels that protect the public health without needlessly endangering economic viability, and will lead to a healthier and more productive citizenry.



The first part of the summary is a general statement of the purpose of the study. It is to determine the effect of the treatment on the response of the subjects.

The second part of the summary is a description of the subjects and the treatment. The subjects were 100 healthy young men, and the treatment was a 10-day course of the drug. The third part of the summary is a description of the results of the study. The results show that the treatment had a significant effect on the response of the subjects. The fourth part of the summary is a conclusion. The conclusion is that the treatment is effective in increasing the response of the subjects.

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