

**Department Of Health And Human Services
National Institutes Of Health
National Institute Of Environmental Health Sciences**

**Minutes Of The National Advisory Environmental Health Sciences Council
February 11-12, 2002**

The National Advisory Environmental Health Sciences Council was convened for its one hundred fifth regular meeting on February 11, 2002, at 8:30 a.m., in Rodbell Auditorium, Building 101, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. The meeting was open to the public from 8:30 a.m. until 5:00 p.m. and on February 12 from 8:00 a.m. until 9:00 a.m. The meeting was closed for consideration of grant applications on February 12 from 9:00 a.m. until 10:30 a.m. Dr. Kenneth Olden presided as Chair on February 11 and Dr. Samuel Wilson presided as Chair on February 12, 2002.

Members Present:

Daniel Baden, Ph.D.
Noreen Clark, Ph.D. R.
Joan Cranmer, Ph.D.
Dale Eastman
Deeohn Ferris, J.D.
George Friedman-Jimenez, M.D.
Michael Gallo, Ph.D.
Frederick P. Guengerich, Ph.D.
Barbara S. Hulka, M.D., M.P.H.
Philip M. Iannaccone, M.D., Ph.D.
Daniel W. Nebert, M.D.
Peggy Shepard
Martyn T. Smith, Ph.D.
Robert D. Wells, Ph.D.

Members Absent:

Michael Karin, Ph.D.
Michael McClain, Ph.D.
Martyn T. Smith, Ph.D.
Hon. Harriett M. Wieder

Ex Officio Members Present:

Kelley Brix, Ph.D.
Eric L. Stephens

Liaison Members Present:

Daniel Acosta Jr., Ph.D.
Michael Galvin, Ph.D.
Robert Spengler, Ph.D.

Members of the Public Present:

None

NIEHS Staff:

Cindy Afshari, Ph.D.

Kathy Ahlmark
Beth Anderson
Lisa Archer
Trevor Archer, Ph.D.
Martha Barnes
Linda Bass, Ph.D.
Sharon Beard
PJ Blachshear, M.D.
David Brown
Gwen Collman, Ph.D.
Allen Dearry, Ph.D.
Dwight Dolby
Dorothy Duke
Thorsten Fjellstedt, Ph.D.
Lerlita Garcia
Janet Guthrie
Jerry Heindel, Ph.D.
Ethel Jackson, D.D.S.
Laurie Johnson
Marian Johnson-Thompson, Ph.D.
Kim Gray Kamins, Ph.D.
Annette Kirshner, Ph.D.
Cindy Lawler, Ph.D.
Charle League
Edith Lee
Carolyn Mason
Patrick Mastin, Ph.D.
Michael McClure, Ph.D.
Sheila Newton, Ph.D.
Liam O'Fallon
Joan Packenham, Ph.D.
Jerry Phelps
Chris Portier, Ph.D.
Jacqueline M. Russell
Anne Sassaman, Ph.D.
Carol Shreffler, Ph.D.
Shobha Srinivasan, Ph.D.
William Suk, Ph.D., M.P.H.
Claudia Thompson, Ph.D.
Fred Tyson, Ph.D.
Bennett Van Houten, Ph.D.
Jose Velazquez, Ph.D.
Charles Wells, Ph.D.
Brenda Weis, Ph.D.
Laura Williams-Boyd
Samuel Wilson, M.D.
Michelle A. Owens
Carolyn Winters
Mary Wolfe, Ph.D.
Geraldine Wolfle

Other Federal Staff:

Robert Dyer - EPA
Patricia Greenwel - CSR, NIH
Peggy Jones - FDA
Rass M. Shayiq - CSR, NIH

Anne Sowell - CDC
Michael D. Waters - EPA

I. CALL TO ORDER AND OPENING REMARKS

The one hundred fifth regular meeting of the National Advisory Environmental Health Sciences Council was called to order by Dr. Olden. Mr. Eric Stephens was introduced as a new ex-officio member representing the Department of Veteran's Affairs.

II. REVIEW OF CONFIDENTIALITY AND CONFLICT OF INTEREST PROCEDURES - Dr. Kenneth Olden

Dr. Olden read the requirements of the Government in the Sunshine Act. All aspects of the meeting were open to the public except those concerned with review, discussion and evaluation of grant applications and related information. The Chairperson explained policies and procedures regarding confidentiality and avoidance of conflict of interest situations.

III. CONSIDERATION OF MINUTES OF FEBRUARY 11-12 , 2001, MEETING

Council accepted the minutes without change.

IV. FUTURE COUNCIL MEETING DATES

May 20-22, 2002 in Research Triangle Park with Retreat.
September 9-10, 2002 (Monday and Tuesday) in Research Triangle Park.
February 10-11, 2003 Research Triangle Park.

V. REPORT OF THE DIRECTOR, NIEHS - Dr. Kenneth Olden

Dr. Olden began his report by commenting on the budget for Fiscal Year 2002, which included a 12.7% increase for NIEHS. Although this budget is good for the Institute, the increase for NIH overall is somewhat offset by the need to accommodate the increased security measures and other activities associated with concerns about bioterrorism in the wake of the September 11 attack on the World Trade Center and letters containing anthrax spores. As a result of the increased security, the environment on the NIH campus and NIEHS as well has changed.

He noted that the first priority for increases for NIEHS is in the Research Project Grants line. However, several of the high priority initiatives-research centers on breast cancer and the environment, the Parkinson's Disease consortium, and expanded activities related to toxicogenomics - will require a significant investment over the next two years. With regard to the Fiscal Year 2003 budget, the President's request is good for NIH and NIEHS and is on target for the 5-year doubling of the budget.

Tentative dates have been set for the Fiscal Year 2003 appropriation hearings, and the House will continue its practice of "theme hearings." This year, NIEHS will be included in the cancer theme, along with the National Cancer Institute and the National Human Genome Research Institute, which will fit very nicely with our interest in genomics and gene-environment interactions. The

hearings will also focus on the translation of research into results-accountability and quantifiable results. Dr. Olden stated that NIEHS needs to move its science into public health practice more quickly, a topic he would like to include at the annual Director's Retreat.

He reported that work done by the New York, New Jersey, and Johns Hopkins Centers and Superfund Program, as well as important contributions of the Superfund Worker Training Program related to the aftermath of the World Trade Center attacks have been well received and resulted in good visibility for the Institute. We have received a supplemental appropriation of \$10.5M for these efforts.

With regard to other Institute activities of interest, Dr. Olden reported the following:

- The December toxicogenomics conference in Bethesda was very successful. We may consider a new journal on toxicogenomics in addition to Environmental Health Perspectives in order to provide a good place for related papers to be published.
- The Institute has formed a Public Liaison Group, which held its first meeting in November. Following this successful first meeting, the group will meet in a retreat setting following the May Director's Retreat.
- A successful conference on the social and ethical implications of the Human Genome Project and the Environmental Genome Project, especially as they relate to people of color, was recently held in New York City. The conference was organized by the West Harlem Environmental Action Coalition, (WEACT) co-sponsored by NIEHS, the US Environmental Protection Agency and Columbia School of Public Health, and emphasized the need to create an informed public around these issues.
- Since the September Council meeting, the Institute has held Town Meetings in Houston, Des Moines, Glendale, CA, Los Angeles and El Paso.
- A brainstorming meeting to discuss bottlenecks in advancing knowledge about breast cancer and the environment will be held in Charlotte, NC in April. The meeting will focus on what is not being done and scientific opportunities.
- New Centers on Children's Environmental Health Research and Prevention have been funded. Two of these deal with autism.
- NIEHS is in the process of recruiting two Associate Directors to assist the current leadership with the vision and scientific leadership of the Institute so that we will be able to take advantage of opportunities as they arise.
- Dr. Tom Goehl has been appointed the new managing editor of Environmental Health Perspectives. The journal will soon begin a new pediatrics section with new members of the editorial board to attract good papers and highlight the Institute's leadership in children's environmental health. The supplements will be replaced by "special issues."

In the discussion that ensued, comments and questions were raised about measures of accountability with regard to translation, opportunities for translation to health care practitioners and how to measure changes in behavior, and the importance of continuing to place high priority on investigator-initiated research.

VI. Report of the Deputy Director, NIEHS - Dr. Wilson

The first part of Dr. Wilson's report centered around the importance of communication of science to the public, and he cited the example of the recent WEACTION conference as a good example. The eleven Town Meetings held since 1998 were also noted as positive means of communication with the benefits of linkages, recognition of environmental health and a venue for dialogue in both directions.

Council members applauded these efforts and commented on the impact of the NIEHS involvement in activities following the World Trade Center attack, where the Centers have been regarded as "honest brokers" and where academic centers have recognized that the community has something to contribute. In addition, the public meetings have filled a void in risk communication, and should continue, as there are a number of remaining issues, including air pollution and stress. Health disparities was another important topic for garnering community interest.

Dr. Wilson then updated the Council on the activities on the Institute of Medicine (IOM) Roundtable on Environmental Health Sciences, Research, and Medicine. Copies of some previous meetings are available, and topics for future meetings are under consideration. Among these are environmental health and chemical and biological terrorism.

VII. "Early Concurrence Module" - Dr. Thorsten A. Fjellstedt

Dr. Fjellstedt briefed Council members on the latest addition to the features of the Electronic Council Book (ECB) which should be in place by the next meeting. This feature will permit concurrence with certain categories of application prior to the Council meeting, and will depend upon procedures and prerequisites agreed upon by the Council and staff. This will allow earlier funding of many applications, a more balanced workload for extramural staff, and the ability to use meeting time to focus on special issues or programs. NIEHS will be one of the NIH institutes to pilot this new ECB module to help work out questions and modifications to the system.

VIII. "Maryland Appeals Court Decision on EPA Lead Abatement Study" - Ms. Deeohn Ferris

Council member Ferris presented a review of the case pending in the Maryland court system involving the Kennedy Krieger Institute's research study of remediation of lead-contaminated housing in Baltimore City. There are a number of important issues in this case related to informed consent and non-therapeutic research on children which may have wider implications. Ms. Ferris stated that there was a wealth of facts at the trial level in which a summary judgment was issued when many, including the appellate court, felt that there was enough disagreement to warrant a full trial. The case has been remanded to the trial court, and a decision there is pending.

IX. "Community-Based Research and Informed Consent" - Ms. Peggy Shepard

Ms. Shepard presented a discussion on developing true informed consent through a Community Advisory Board.

The Council discussion that followed the presentations of Ms. Ferris and Ms. Shepard revolved around the outcomes of non-therapeutic research on children, information provided to parents during a study, and the challenges of observational vs. interventional research. It was suggested that the grantees under the NIEHS Environmental Justice program have some discussion regarding the role of communities in research, specifically related to Institutional Review Boards and Community Advisory Boards. Dr. Olden asked that Council member Dr. George Friedman-Jimenez and Dr. Allen Dearry of the Division of Extramural Research and Training form a subgroup to study recommendations regarding community-based research.

X. "Toxicogenethics: Ethical Issues at the Intersection of Genetics and Environmental Health Research" - Dr. Richard R. Sharp

Dr. Sharpe began with the introduction of a new term, "toxicogenethics," which he described as ethical issues at the intersection of genetics and environmental health research. He described the history of the ELSI, or ethical, legal and social impacts, program associated with the Human Genome Project, some critiques of its activities and focus over the past decade, and the unique features related to toxicogenomics. These include questions related to social justice (what types of research should be carried out?) and what people need to know in order to make informed decisions (autonomy). In particular, how do scientists best present both the promise and the limitations of toxicogenomics to the public without misunderstandings? How might toxicogenomics information be used in ways that are not morally problematic? How will knowledge of genetic susceptibility to environmental agents affect assignment of responsibility for poor health outcomes?

The abstract of Dr. Sharp's presentation is found in Attachment B.

XI. "Toxicogenomics and the Workplace" - Mark A. Rothstein, J.D.

Mr. Rothstein's presentation covered two aspects of the legal implications of genetic/genomic research: workplace regulation and discrimination. An abstract of his presentation is found in Attachment C. In the discussion on workplace regulation, he addressed the questions of regulation in the face of scientific uncertainty, balancing the benefits and burdens of regulation, autonomy vs. paternalism in the workplace, and balancing the rights of employees and employers. The questions regarding discrimination are less clear, since the Americans with Disabilities Act does not cover situations in which there is increased risk but no actual disease or disability.

XII. "Local Communities/Common Concern: The Social Science of Involving Communities in the Research Process" - Dr. Morris W. Foster, Ph.D.

Dr. Foster's remarks focused on three major themes: 1) Why studying local communities can be useful in addressing more general questions; 2) How qualitative social science methods can be validated and used; and 3) The relevance of social science to health science.

In studies in communities, Dr. Foster commented on the advantages and problems with "representativeness." However, the community context is necessary for good social science and

good social science that studies local communities can be validated for larger communities. In addition, social science is necessary for good biological science that takes environmental factors into account.

An abstract of Dr. Foster's presentation is found in Attachment D.

XIII. "NIEHS Publication Tracking System" - Dr. Ben Van Houten, Ph.D.

Dr. Van Houten presented to the Council a new tool developed by staff of the Program Analysis Branch, Division of Extramural Research and Training, and the Computer Technology Branch, Office of Management, Scientific Publication Information Retrieval and Evaluation System (SPIRES), and acknowledged the contributions of these staff in the effort. This is a web-based tool to follow publications and assess productivity of grantees receiving research support from the NIEHS. Its use of bibliometric analysis and peer review is a good tool in evaluation. The program links the NIH information system "IMPAC II," which contains information on all funded grants, with the National Library of Medicine's data base of publications. Dr. Van Houten discussed the strengths and limitations of SPIRES and presented a demonstration of its capabilities.

Council members congratulated Dr. Van Houten and the Institute on this new tool, and asked questions about the use of the data gleaned from the analyses, the ability of the system to compare with other NIH institutes (not currently available), but also cautioned against inappropriate comparisons as well.

XIV. Report of the Director, DIR - Dr. Lutz Birnbaumer, Ph.D.

The written report from the Division of Intramural Research can be found in Attachment E. Dr. Birnbaumer, in his first report as Scientific Director, focused on the status of new recruitments and the track record of NIEHS fellows in NIH-wide programs to recognize post-doctoral research accomplishments.

XV. "The Role of Environmental Exposures in the Fetal Basis of Postnatal Pathophysiology" Concept Clearance - Dr. Jerrold Heindel, Ph.D.

Dr. Heindel presented an overview of the Institute's extramural activities in developmental toxicology, focusing on critical periods of exposure and outcomes. He then discussed the concept clearance "The Role of Environmental Exposures in the Fetal Basis of Postnatal Pathophysiology" and strategies for developing this area of research. The document is found as Attachment F. Council members were supportive of this concept as a long-term investment for the Institute. Staff were encouraged to consider eye development, neuroendocrine connections, and the role of endocrine disruptors.

XVI. "Breast Cancer and the Environment" Concept Clearance - Dr. Gwen Collman, Ph.D.

Dr. Collman described the Institute's historical involvement in research on breast cancer and the environment and plans for future activities related to recent Congressional interests and language

in the Fiscal Year 2002 NIEHS appropriations bill. The concept paper for these activities is found as Attachment G. The first step will be the brainstorming meeting in April mentioned by Dr. Olden in his report. Council discussants supported the concept, especially working with advocacy groups at all stages of development and assessment of the program.

XVII. "Oceans and Human Health" Concept Clearance - Dr. Allen Dearry, Ph.D.

Dr. Dearry reviewed for the Council a number of meetings and workshops held over the last several years dealing with the topic of oceans and human health, the most recent of which was held in December at NIEHS. This summary is included in the concept document found in Attachment H. The concept for future NIEHS activities revolves around an interdisciplinary approach that includes co-sponsorship with the National Science Foundation. The proposed new centers would complement the existing Marine and Freshwater Biomedical Research Centers. Council reviewers and members were supportive of the plans outlined in the document and suggested that staff consider inviting other agencies with interests in oceans and oceanography to participate

At the end of the staff presentations, council voted approval of all three concepts.

XVIII. Report of the Director, DERT - Dr. Anne P. Sassaman, Ph.D.

The complete report of staff activities and significant papers of the Division of Extramural Research and Training can be found in Attachment I. Dr. Sassaman called the Council's attention to these, noting some particular items and commenting that the papers are one of the primary "products" of the Institute's extramural research investment.

Her presentation focused on three areas, the first of which was a review of Fiscal Year 2001 activities and expenditures. She and Council members discussed the success rate as a measure of state of the program and strategies for dealing with the end-of-doubling era. The statistics for this part of the presentation are found in the attached report.

The second item was a preview of the new extramural loan repayment program for clinical and pediatric researchers and the Institute's plans for awarding its \$226,000 allocation for this fiscal year. The program will be managed through the NIH Office of Loan Repayment, but individual applications will be assigned to institutes on the basis of the source of funding for review and prioritization. Council will receive a report in May on the outcome of this process.

The final item in the DERT Director's Report was the annual review of Council Delegated Authorities/Guidelines for Staff Actions. Proposed changes were reviewed and approved by Council. This document is found as Attachment J.

CLOSED PORTION OF THE MEETING

This portion of the meeting was closed to the public in accordance with the determination that it was concerned with matters exempt from mandatory disclosure under Sections 552b(c)(4) and

552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

There was a discussion of procedures and policies regarding voting and confidentiality of application materials, committee discussions and recommendations. Members absented themselves from the meeting during discussion of and voting on applications from their own institutions, or other applications in which there was a potential conflict of interest, real or apparent. Members were asked to sign a statement to this effect.

XIX. REVIEW OF APPLICATIONS

The Council considered 265 applications requesting \$58,693,304 in total cost. The Council recommended 173 applications with the total cost of \$41,424,132.

XX. ADJOURNMENT OF THE NAEHS COUNCIL

The meeting was adjourned at 10:30 a.m. on February 12, 2002.

ATTACHMENTS:

- A. [Council Roster](#)
- B. [Toxicogenethics: Ethical Issues at the Intersection of Genetics and Environmental Health Research](#)
- C. [Toxicogenomics and the Workplace](#)
- D. [Local Communities/Common Concerns: The Social Science of Involving Communities in the Research Process](#)
- E. [Report of the Director - DIR](#) In [Adobe Acrobat](#) Format
- F. [The Role of Environmental Exposures in the Fetal Basis of Postnatal Pathophysiology Concept Clearance](#) - Dr. Heindel
- G. [Breast Cancer and the Environment Concept Clearance](#) - Dr. Collman
- H. [Oceans and Human Health Concept Clearance](#) - Dr. Dearry
- I. [Report of the Director - DERT](#)
- J. [Annual Review of Council Delegated Authorities/Guidelines for Staff Actions](#)

Ethical Issues in Toxicogenomics

Richard R. Sharp, PhD
Biomedical Ethicist
National Institute of Environmental Health Sciences

Scholars in the fields of ethics, law, philosophy, and public policy have been highly interested in the social implications of the Human Genome Project and related research in human genetics. Much of the resulting scholarship and research in these fields has examined challenges surrounding the development and integration of predictive tests for genetic diseases and disease susceptibilities. Prominent topics in this literature include: the role of genetic counseling in patient decision making, best practices for informed consent, consumer and physician education regarding genetic influences on disease, impact of genetic testing on family relationships, and protections against genetic discrimination in insurance and employment contexts. To a much lesser degree, scholarship in the humanities and research in the social sciences also has examined ethical, legal, and social issues surrounding the application of genetic information and diagnostic tests in non-clinical settings. For example, researchers have considered issues surrounding the use of DNA-based tests to determine paternity in child-custody disputes. The application of genetic tests to link criminals to forensic evidence has also been studied. More recently, there has been an emerging body of literature on tests for genetic sensitivities to occupational and environmental agents. In general, however, scholars have given surprisingly little attention to non-clinical applications of the tools of modern genetics.

One place where this lack of research on the ethical and social dimensions of applying genetic technologies in non-clinical contexts is particularly striking is in the toxicological sciences. To date, there have been no significant studies of ethical, legal, policy, and regulatory implications surrounding the application of genetic information and technologies to hazard identification, risk assessment, risk management, and environmental regulation. This is discouraging because the elucidation of mechanisms by which genes influence response to environmental toxins will transform the practices of risk assessment and environmental regulation significantly. For example, genetic tests might be used to identify hypersensitive subgroups in the population or reveal presently unknown environmental hazards. These and other possibilities argue strongly for the need to study ethical, legal, and social dimensions of the coming "genetic revolution"; in the toxicological sciences.

This presentation will explore ethical and policy issues in the application of genetic technologies to hazard identification, risk assessment, risk management, and environmental regulation. Emphasis will be placed on the emerging field of toxicogenomics, defined as the application of genomic technologies to the identification and understanding of human and environmental toxicants. If genomic technologies are to be successfully integrated into ongoing risk-assessment and risk-management efforts, the social impacts of these applications must be carefully studied and thoughtfully addressed.

Toxicogenomics and the Workplace

Mark A. Rothstein, J.D.
Herbert F. Boehl Chair of Law and Medicine
Director, Institute for Bioethics, Health Policy and Law
University of Louisville School of Medicine

New discoveries in toxicogenomics are likely to have significant consequences for certain employers and employees. In legal terms, there are two sets of issues: (1) regulatory issues (mainly under the Occupational Safety and Health Act); and (2) discrimination issues (mainly under the Americans with Disabilities Act).

Genetic predisposition to occupational illness is not an issue that Congress considered in enacting the OSH Act in 1970. Information regarding varied sensitivity to industrial toxins, however, has been known for many years. To what extent should our ability to make more precise risk assessments affect standard setting, medical screening, job assignment, warnings to employees, or enforcement actions against employers? Although there is little definitive precedent, there are some cases to guide the analysis.

The question of whether the ADA applies to asymptomatic individuals who are at a genetically increased risk of disease is a hotly debated issue. While the statute makes no reference whatsoever to genetics, the Equal Employment Opportunity Commission, which is charged with enforcement of the ADA, issued an interpretation in 1995 that discrimination based on genetic predisposition would violate the ADA. This interpretation is not binding on the courts, and Supreme Court decisions in 1999 and 2002 cast great doubt on whether this interpretation would be followed. Related issues to be resolved include whether "voluntary" measures to inform employees of their genetic risks and removal of employees from exposure when they constitute a "direct threat" to themselves would violate the ADA.

**Local Communities / Common Concerns:
The Social Science of Involving Communities in the Research
Process**

Morris W. Foster
Department of Anthropology
University of Oklahoma, Norman
Oklahoma Medical Research Foundation, Oklahoma City

The great strength of ethnography is its ability to elicit fine-grained information about particular communities. The great limitation of ethnography is the difficulty in generalizing that necessarily local information to speak to regional, national, and global issues. As health research increasingly embraces ethnographic methods, the problem of generalizeability becomes central. We value local detail, but we can't investigate every local community. How, then, can the study of local communities be made relevant to questions that apply to larger-scale, often heterogeneous populations?

Two strategies suggest themselves. Both begin by doing sufficient background research to conceptualize the larger population at issue as a whole, and specifically to understand how it is internally organized into social networks and subgroups. The rationale for obtaining this understanding in the first instance is to then conduct the community engagement as a purposeful process--that is to say, to engage the community in a discussion of questions of interest to researchers by approaching the appropriate social actors and groups that the community itself recognizes as composing its primary internal divisions. Anthropologists often use participant-observation as a means for gaining this background knowledge.

Populations, however defined (and definitions used by both outsiders and insiders often are somewhat arbitrary or imposed), and the communities that comprise them reflect a variety of internal social dynamics. Anthropologists have learned to use those existing internal means for collective interaction, decision-making, and even disagreement as both an appropriate and convenient way to address questions to a group of people who share a common label. In this manner, we learn more about how that label is applied or claimed and what it implies for the questions in which we are interested. We also often learn about different questions that are of more primary interest to community members, questions that may cause us as researchers to reorient our interests.

In the first strategy, researchers attempt to contact and involve the leaders of

formally organized subgroups that approximate the range of social divisions within the larger population (i.e., social, religious, fraternal, etc. groups) in an ongoing dialogue. That dialogue then serves as the basis for understanding community perspectives. In the second, more ethnographic, strategy, researchers identify several local geographic divisions of the larger community that constitute relatively small sub-communities in themselves (e.g., neighborhoods) and engage them in the same manner, though concentrating on ordinary members rather than leaders.

The difficulty with the first approach is that formally organized community groups and their leaders may not provide an accurate reflection of the full range of views within the larger group. The difficulty with the second approach is that views within the larger community may vary significantly from one locality to another. However, both of these difficulties can be overcome by using focus groups and surveys to randomly spot-test the validity of those necessarily limited findings in other segments of the larger community, so long as those focus groups and surveys use samples that reflect a demographic cross-section of the larger population or using similar sampling methods in administering an individual survey instrument. There are standard methods for determining how many focus groups or individuals surveyed will constitute an appropriate sample for validation, depending on the size of the larger population.

Another useful means for engaging a community, for taking its temperature during that process, and for helping validate the findings of a consultation is a public meeting. There are two ways to think about organizing a public meeting: (1) securing a meeting space in the community and calling a special meeting open to all members just to discuss the project; or (2) securing a place on the agenda of a regularly-scheduled public meeting to discuss the project. The former approach requires some means for motivating attendance and participation that may result in a very self-selected audience (with either or both strong proponents or strong opponents in attendance but with few members who are in the middle). The latter approach may play to an audience that is self-selected for quite different reasons (i.e., the main purpose of the regular meeting) and so not be much engaged in the issues of interest to researchers. Thus, public meetings, while be useful as supplements to the process outlined above, should not be relied on as the primary means to accomplish community engagement.

The outcome of the researcher's discussions with the community must be documented and made available to others, usually through the scholarly literature where it is subject to peer review. As part of the documentation, the researcher should describe the methods that were used in the engagement (i.e., interviews, forums) and the rationale for the choice of community representatives consulted. The researcher should also provide a summary of the views of the individuals and groups involved in the process. The researcher must also put a plan into place for long-term follow-up with each participating community.

Concept Clearance for The Role of Environmental Exposures in the Fetal Basis of Postnatal Pathophysiology

Introduction

It is recognized that between 2% and 5% of all live born infants have a major developmental defect. Approximately 40% of these defects are thought to be due to the effect(s) of an adverse exposure of a genetically pre-disposed fetus to intra-uterine environmental factors. Exposure to environmental agents during development can result in altered growth overall, structural malformations, functional alteration and/or death of the embryo/fetus. In addition, 30-40% of the four main adult human cancers have been recently reported to be the result of environmental factor(s) exposures. Such exposures could include the possibility that a pre-disposition to the adult cancer originates in the embryo-fetus period of the life span. These toxicant-induced pathogenic responses are most likely the result of altered gene expression associated with altered cell production and cell differentiation involving altered replication/cell cycle/cell proliferation, molecular secretion/endocytosis/uptake/migration/adhesion or signal transduction processes, patterns of apoptosis, or combinations thereof involved in the establishment of cell lineages leading to the structural and functional character of the tissues, organs, and systems that arise from these lineages.

The purpose of this concept proposal is to address an important and emerging area of developmental toxicology: the effect of *in utero* exposures that cause permanent functional changes that are not overtly, grossly teratogenic and that result in increased susceptibility to disease/dysfunction later in the life span. It is becoming increasingly more apparent that there is an environmental component to nearly every disease. In some cases the environmental trigger is an exposure experienced in the adult environment. However, it is now clear that in many cases the fetus is more sensitive to the same environmental insults and that the effect of exposures during development may have a far more detrimental effect on the etiopathology of the disease.

The NIEHS has a significant program that addresses the role of developmental exposures on structural malformations i.e., classical birth defects. Recent NIEHS leadership in this area includes an RFA entitled, "Developmental Toxicology Exploratory (R21) Research Grants" that is being presented at this meeting of the NAEHS Council. However, there has been minimal scientific activity and no initiatives in the area of the role of environmental agents in causing functional changes that are expressed as an increase in disease/dysfunction later in life. The new high-throughput functional-genomic, metabonomic, proteomic, and

bioinformatic technologies now offer for the first time the opportunity to pursue research questions in this area. The importance of exploring this promising area were highlighted by expert presentations at the 2000 and 2001 DERT annual science retreat. The underlying scientific hypothesis has been developed by epidemiology studies and emphasized by Dr. David Barker in the U.K. This hypothesis, named the Barker Hypothesis, proposed that pre-natal origins of health and disease is one of the most important issues that affects our lives and that of our children. Studies by other researchers have continued to support this hypothesis. The DERT retreat speakers' called attention to Dr. Barker's work and the overwhelming epidemiological and clinical evidence that intrauterine conditions can permanently alter the development of tissues and organs by a currently cryptic mechanism that leads to an increased susceptibility to certain diseases and disorders. He has shown that during development fetuses respond to adverse conditions by favoring the metabolic demands of the growing brain/CNS and heart at the expense of other tissues. The growing brain/CNS and heart tissue may not, however, escape entirely unscathed. The long-term consequences of this response are that the fetus is protected from death, is live-born, but is more prone to diseases later in life.

The earlier Barker Hypothesis studies concentrated on grossly altered nutrition as the source of the stress during development. These studies showed via epidemiology studies that low birth weight, small for gestation age, frank intra-uterine growth retardation (IUGR) or clinically abnormal thinness at birth strongly predicts the subsequent occurrence of hypertension, hyperlipidemia, insulin resistance, type 2 diabetes, ischemic heart disease, breast cancer or prostate cancer in adult life. Fetuses that are clinically malnourished during the first trimester of development are three times more likely to be obese as adults. Evidence has been presented in human populations that gross, heavy exposure to PM10 air pollution containing carcinogenic PAHs can be correlated with increased IUGR with a peak impact in the earlier portion of the first trimester - a most vulnerable period of the cell lineage expansion, differentiation, and cell interactions events of organogenesis and first growth.

The concept of fetal programming of structural-functional formations during development has been proposed to explain these findings and the resultant research area is referred to as Fetal Basis of Adult Disease (FBAD) research. Programming is the term used to describe lifelong changes in function that follow a particular event in an earlier period of the life span. While epidemiology studies have identified the phenomenon of metabolic programming, little is known about the mechanism(s) by which fetal insults lead to altered programming and to disease later in life. In addition, emphasis thus far has been on alterations in nutrition during development with virtually no focus on the role that exposures to environmental agents, such as air or water pollution, either alone or in combination with qualitative alterations in macro- or micro-nutrition (i.e. soy protein, phytoestrogens, isoflavones or other chemicals in herbal supplements or dietary sources), might have on this phenomenon. There is, however, evidence that some environmental agents, especially those with endocrine agonist or antagonist activity, may alter developmental programming via alteration in gene expression or gene imprinting that do not result in malformations but in functional deficits that do not become apparent until later in life. A major Trans-NIH workshop (Diet, DNA Methylation Processes and Health, August 6-8, 2001) co-sponsored by the NIEHS, produced reports suggesting that an aberrant genomic imprinting mechanism involving DNA methylation could underlie the aberrant physiological effects noted. It is not clear at present whether these epigenomic modifications involve epistasis (gene silencing) or inappropriate gene

expression events. Additional evidence supporting the Barker Hypothesis was presented at the Developmental Psychology Society Winter Conference, co-sponsored by the NIEHS, on January 12-14, 2002.

In terms of the Barker Hypothesis, the three disease areas where there are the most compelling preliminary data involve:

1. the reproductive tract,
2. the pulmonocardiovascular system, and
3. the brain/CNS systems.

In the reproductive tract, the classic example of this phenomenon in the environmental area is the DES story. In humans, *in utero* exposure to DES leads to an increase in vaginal adenocarcinoma around the time of puberty. In mice, neonatal DES exposure leads to an increase in uterine adenocarcinoma in adulthood. While the direct connection has not been made between *in utero* programming changes due to DES and later life disease, it is known that DES (in the animal studies) results in altered gene expression in the uterus that is irreversible without any noticeable gross alterations in uterine morphology. Other examples in the reproductive area include developmental exposures of the monkey to androgens that leads to polycyclic ovary syndrome-like effects in the adult and data (still considered controversial) showing that environmental estrogens, such as DES, methoxychlor and bisphenol A, cause alterations in gene expression in the rat prostate that are irreversible and are correlated with increased prostate cancer.

Cardiopulmonary diseases in postnatal life have also been linked to prenatal exposure. The most well known example is the association between low birth weight (which is associated with poor maternal nutrition and perhaps corticosteroid exposure) and cardiovascular disease (e.g., myocardial infarcts) and predictors of future cardiovascular disease, such as hypertension and atherosclerosis, and complex metabolic disease, such as diabetes. In addition, studies have shown that maternal smoking is associated with deficits in lung function and with asthma symptoms in the offspring. Data indicate that these associations are independent of smoking status after birth.

Some forms of neurodegenerative disease may have their origins in *in utero* exposures. For example, there is preliminary evidence that a bacterial stimulus (endotoxin) can produce cytokines that impair the development of the mesencephalic dopaminergic systems during pregnancy. This attenuation of the dopamine neurons during fetal development leaves the offspring with fewer dopaminergic neurons at birth and at possible increased risk for Parkinson's disease in later life. In a similar vein, there is preliminary evidence that exposure to environmental neurotoxins during dopaminergic development enhances the susceptibility to accelerated dopaminergic cell death during aging via the common molecular mechanism(s) of the alteration of stress-activated signal transduction pathways, expression of differentiation transcription factors, survival factors or phenotype marker proteins in the nigral dopaminergic neurons. In all instances data is needed to show that the *in utero* exposures actually lead to an altered programming at the molecular level and that the disease/dysfunction is a direct result, albeit, temporally discordant in its onset and/or progression, of that altered programming.

Research Goals and Scope

Based on the epidemiology data that support the Barker Hypothesis and the

preliminary data showing alterations in gene expression and imprinting due to *in utero* exposures to some environmental agents, we propose that exposure to certain environmental chemicals as well as altered nutrition, or in combination with altered nutrition, will in some situations, not lead to easily identifiable structural malformations, but instead to alterations in developmental programming expressed as a permanently altered gland, organ or system potential. These states of altered potential would be a result of changes in gene expression, imprinting, and the underlining methylation-related protein-DNA relationships associated with chromatin remodeling. These effects may occur in a time specific (i.e. vulnerable window) and tissue specific manner and such alterations may be irreversible. The end-result is an animal that is sensitized such that it will be more susceptible to diseases later in life. A second part of this hypothesis is that the environmental insult could act via a one hit or two/three hit scenario. That is, there could be an *in utero* exposure that would lead by itself to pathophysiology later in life or there could be *in utero* exposure combined with a neonatal exposure (same or different compound(s)) or adult exposure that would lead to the pathophysiology. A third part of this hypothesis is that the pathophysiology or functional change that results from the exposures/insult could lead to: A) the occurrence of a disease that otherwise would not have happened, B) an increase in a disease that would normally be of lower prevalence or C) either an earlier onset of a disease that would normally have occurred or an exacerbation of the disease. Finally, the pathophysiology could have a variable latent period from onset in the neonatal period, to early childhood, to pubertal, to early adulthood to late adulthood depending on the toxicant, time of exposure and tissue/organ affected and potentially transgenerational effects.

The very nature of the problem mandates that the studies related to this initiative, at some time, involve whole animal developmental exposures with analysis of the fetus, embryo and pups and well as later life disease/ dysfunction incidence. These analyses can be done using transgenics, model organisms, or rodent models. Such research must be encouraged to use environmentally relevant doses, dose response curves and the examination of the relationship between the molecular mechanism proposed and the disease/dysfunction studied in a cause and effect manner.

This initiative is timely as the new technologies of gene expression profiling, epigenetics and methylation for the first time allow examination of alterations in programming. The use of these technologies also allows assessment of *in utero* exposure to environmental agents and to show a direct correlation and eventually a cause and effect relationship to the alterations in gene expression (either increased, decreased or inappropriate timing) to alterations in signal transduction pathways and alterations in growth factors and cytokines and hormones that lead to a specific disease or dysfunction that occurs later in life.

This novel and innovative approach to pathophysiology has the potential to not only link *in utero* and neonatal exposure to environmental agents to certain of the most prevalent diseases of our time but to also show cause and effect relationships as a view to exposure assessment. Such studies may, for the first time, offer real time evaluation of exposures and exposure outcomes. The data generated by this program will also be important to deciphering gene-environment interactions in disease and for understanding the role of polymorphisms in susceptibility to disease.

Program

We propose a broad-based, two phased, program that will integrate multiple extramural programs in pathophysiology and that will potentially encompass certain of the most prevalent human diseases and disorders. This will be a long-term (5-7 years), multi-phase program that will utilize several NIH grant mechanisms including RFAs and Program Announcements, with or without a set-aside, grantee meetings and conferences.

In order to focus this program, we propose that the first initiative should focus on only the three areas that have the most preliminary data and, thus, show the most promise of success: the reproductive tract, the pulmonocardiovascular system, and the brain/nervous system.

Other areas of opportunity may be the focus of later individual initiatives and these include immunity and autoimmunity, gastrointestinal/obesity, other endocrine, and musculoskeletal/bone. We also propose that the first initiative should focus on *in utero* exposures and adult onset diseases. As warranted, subsequent expansions may also include the fetal basis of early childhood and pubertal diseases as opposed to adult onset diseases.

Applicants to the initial phase of this program will be asked to link *in utero* and/or neonatal exposures during critical windows of development to changes in gene expression that are tissue specific (reproductive, cardiopulmonary and brain) and irreversible. These changes in gene expression will then be measured in the adult and correlated with the diseases/dysfunction studied with or without additional adult exposures. Thus the purpose of the initial phase of this program is to develop the preliminary data for a role of developmental/neonatal exposures to specific environmental stressor in the initiation or exacerbation of diseases of long latency.

The second phase of this program will then focus on supporting the advanced development of the most promising research generating the crucial data to associate exposures and disease/disorders by studies that will actually prove cause and effect. A future phase may also expand the focus to other diseases/dysfunctions and shorter latent periods to include childhood and pubertal diseases. This later part of this program will have an interface with the NIEHS environmental genome project (EGP), toxicogenomics, and National Toxicology (NTP) projects, especially as there may be a role for genetic polymorphisms that will alter the expression of the adult diseases. It will also interface with the Molecular Epidemiology program as well.

Mechanism

The first phase of this program is expected to be an R21/R01 RFA entitled, "Role of Intrauterine Environmental Exposures in the Development of Adult Pathophysiology" which will request applications addressing one of the three initial emphasis areas, reproductive, pulmonocardiovascular and brain with a focus mainly on adult onset diseases. A clear target area in the pulmonocardiovascular area, for example, as identified in the 2001 DERT Science retreat report, would seek projects focused on cardiac aberrations associated with early gestational environmental agent exposures.

Timetable

Proposed Release Date: April 2002

Proposed Receipt Date: August 2002

Council Review: Feb 2003

Anticipated Funding Date: April 2003

As mentioned above, It is anticipated that there will be follow up activities to expand this important emerging area that affects so many diseases and dysfunctions, including a second initiative to follow after 2 years to sustain and stimulate the best science being accomplished as well as grantee meetings and an evaluation conference and report to the NAEHS Council at the end of the 5th year of this program.

Concept Clearance for Breast Cancer and the Environment

Background

Despite decades of research on the causes of breast cancer, the etiology of this disease, which affects over 200,000 U.S. women per year, remains elusive. Approximately ten years ago, women with breast cancer and those who support them started asking scientists to consider the environment in their search for causes. At that time the leading theories included those related to ethnic origin, social class, family history, reproductive factors and genetics. None of the hypothesized risk factors were easily modifiable. Women were concerned then, and continue to be concerned now, about the host of commercial and industrial chemicals, which pollute our environment, and their exposures to these chemicals. At the same time, an early report emerged showing a threefold risk of developing breast cancer in women exposed to DDT in a cohort of women in New York City. Studies in various wildlife species were showing hormonally related changes from exposures to chemicals that mimic the effects of estrogen in the natural environment. Ten years ago they asked why scientists were not studying these exposures in relation to breast cancer risk.

In 1992, NIEHS and NCI collaborated on several research programs that were developed to specifically address these concerns. We were interested in the causes of apparent high prevalence of breast cancer in the Northeastern Region of the U.S. and also specifically in Long Island, NY. Many epidemiologic studies were launched looking at possible chemical exposure to DDT and PCBs , chemicals that were used in high concentrations in this area of the country during the time period that the women were in their teenage and early reproductive ages. Several biologically plausible theories were put forth dealing with the possible role of environmental estrogens (chemicals which mimic the activity of estrogens and bind to the estrogen receptor) and the role of electric magnetic fields (mediated through melatonin) in the etiology of breast cancer. Over the last ten years NIEHS has stimulated this field by supporting research focused on endocrine disrupting chemicals, timing of exposures to environmental toxicants and breast cancer risk and genetic susceptibility to breast cancer.

From these studies, we have learned that using currently available epidemiologic and exposure assessment techniques, it appears that DDT and PCBs exposures as measured in adulthood are not related to breast cancer risk in women living in countries where these chemicals are banned. In contrast, there are some studies suggesting elevated risk in women living in some countries where spraying with DDT continues today. We have learned that prenatal exposures to dioxin do have

an effect on mammary gland development. And we continue to explore the perturbations in molecular mechanisms of mammary gland development in experiments using PAHs, DDT, and PCBs as exposures. The NTP rodent bioassay suggests that there are about 40 chemicals that may cause breast cancer. Many are industrial exposures and are therefore difficult to study in women. Recent evidence points to other chemicals such as bisphenol-A, atrozine, PhIP, and other polyaromatic hydrocarbons that may affect mammary gland development by changing the pattern of branching in the breast affecting primarily the terminal end buds. Scientists are also currently exploring how chemical exposures may change the hormonal milieu and how these changes can impact on breast cancer risk.

An important theme in this emerging field is that the developing breast may be more susceptible to the effects of environmental agents during critical windows during the life span. Exposures during these periods may increase the risk for breast cancer later in life. It is well known that girls who were less than 14 years old at the time of the atomic bomb in Hiroshima have an increased risk of breast cancer. It has been suggested that early cigarette smoking in adolescence may increase risk. Recent work in Michigan has shown that girls whose mothers were exposed to PBB during and after their pregnancy have an earlier onset of menarche. Chemical exposures such as atrozine may cause premature ovarian senescence, which affects the amount of circulating estrogen in the mice.

As the decade has progressed many new scientific tools have become available which can enhance our ability to study the role of chemical and physical exposures and lifestyle factors in breast cancer risk. The identification of the human genome, the development of transgenic mouse models and their use in molecular toxicology, the development of microarray chip technology allowing for the creation of the field of toxicogenomics, and new analytic techniques to quantify exposures to environmental chemicals, all pave the way for extending and expanding the vigor with which we can attack these scientific questions.

In the FY 2002 appropriations bill urged NIEHS to create a network of multidisciplinary research Centers which would bring together the knowledge and manpower needed to pursue important research questions in mammary gland biology, carcinogenesis and environmental health sciences. Congress encouraged NIEHS to study the Department of Defense Congressional Mandated Breast Cancer Research Program and use it as a model to include the participation of the breast cancer advocacy community in the design and development of this program.

Partnerships with the Breast Cancer Advocacy Community

NIEHS has been a pioneer in developing research programs that take full advantage of the critical knowledge that communities affected by environmental pollution and unacceptable disease burden possess. Our translational research program which comprises programs in environmental justice, community based participatory research, the Centers for Children's Environmental Health and Disease Prevention Research Program all utilize strong partnerships between community, researchers and health professionals in the design and implementation of environmental health sciences research conducted. The NIEHS Core Centers program has a strong community outreach and education program as well, which fosters linkages between the academic institutions and communities and governmental policy makers.

In the development of this new program on Breast Cancer and the Environment, NIEHS is poised to work closely with the breast cancer advocacy community in order to forge a strong partnership. NIEHS is interested in conducting a series of dialogs with women in these grassroots groups to better understand the concerns of the women, and to engage them in the process of developing the components of the program. Through these and other interactions we will seek advice, consultation and recommendations on a number of key issues related to this program. Any research activities would include strong local partnerships between community groups, scientists, clinicians, and other stakeholders across the country. They may include the formation of local community advisory boards, community participation in the research itself, and solicitation of advice and direction from breast cancer survivors and advocates in the local centers. It is expected that the breast cancer advocacy community would also play a critical role in the translation and dissemination of important research findings to policy makers, the health care community and to the women at risk.

Proposed Strategy

Over the next year, we anticipate conducting several workshops that will bring together leaders in the variety of fields of science with leaders in the breast cancer advocacy community to discuss topics that are relevant to research on breast cancer and the environment. The Division of Extramural Research and Training recently (November 2001) conducted a scientific retreat to discuss this area and some recommendations were made regarding topics for further discussion and input. These include:

- A full exploration of the response of the mammary gland (changes in structure, genetic control of development, etc.) to exposures during different windows of susceptibility. This will help identify gaps in our knowledge relative to the toxicology of various agents after in utero, pubertal, and reproductive exposure.
- Assessment and development of existing and new animals models (including standard rodent bioassays and new transgenic models) which will enhance our ability to study how and when environmental agents target and affect the mammary gland.
- Creation of databases that can be used to characterize the effects of key chemicals and classes of chemicals on the molecular architecture of the mammary gland across different life stages.
- Integration of existing knowledge of the genetics of breast cancer with emerging information on how environmental response genes affect the carcinogenic process.
- Molecular epidemiology studies of gene environmental interaction with regard to breast cancer.
- Improvements to exposure assessment methodologies to refine estimates of body burden of key classes of chemicals and other exposures of interest across the life span.
- Community based participatory research in communities at highest risk.
- The role of the social environment and its interaction with physical and chemical exposures on the etiology of breast cancer.

Summary

In the last decade, some research has been conducted the role of environment exposures as likely causes of breast cancer, but it has just scratched the surface.

Although some study findings have not shown risk in human populations, the overall effects of the environment on the mammary gland are viewed by some scientists as an open question and an area ripe for further investigation. There are still concerns by breast cancer survivors and advocates as to why more has not been done and why more scientific information is not available. Many scientific questions remain unanswered and have not been addressed in a coordinated targeted effort. With recent scientific advances in molecular and environmental health sciences new opportunities exist to fill these gaps. NIEHS will be embarking on a program development effort in partnership with scientists and leaders from the breast cancer advocacy community and will use information from all stakeholders to create a scientific research program. The shape and specific focus of the program will take form as we meet with the respective parties and listen to their input.

Concept Clearance for Oceans and Human Health FY 2003

Background

NIEHS views 'oceans and human health' as both an opportunity and a challenge. Oceans have become conduits for a number of environmental threats to human health. At the same time, oceans harbor diverse organisms that show great promise for providing new drugs to combat cancer and fight infectious diseases. To guard against such health threats and to take advantage of the medicinal benefits that oceans might provide, the impacts of the oceans on human health should be more fully explored.

For the past two decades, the NIEHS has supported a set of Core Centers devoted to Marine and Freshwater Biomedical Sciences. This small but unique resource within the NIH has conducted innovative research focused on development and application of aquatic organisms as models of human health effects resulting from exposure to environmental toxicants. This is a highly productive program, but its scope does not address the gamut of connections between the oceans and human health, ranging from marine processes that threaten public health to the contributions of marine biodiversity to biomedicine. Since the International Year of the Ocean in 1998, the NIEHS has participated in a number of interagency activities, workshops, and IOM panels designed to enhance our understanding of the ocean's role in human health. As a result of these efforts, the NIEHS has been developing ties with the National Science Foundation (NSF) Division of Ocean Sciences to address scientific needs related to oceans and human health (OHH). A joint program between the two agencies in OHH is a logical step for both NIEHS and NSF, in light of shared and complementary interests in this field and their respective research strengths. NSF brings its expertise in ocean biology, chemistry and physics, while NIEHS provides its expertise in environmental health research, prevention research, and ties to the public health community.

To update these shared research interests, NIEHS and NSF hosted a roundtable on OHH in December 2001. Experts in epidemiology, pharmacology, biological oceanography, geochemistry, and biochemistry participated in this meeting. As a result of this discussion, the following research areas were identified as being of high priority.

Research Areas

Combating the spread of harmful algal blooms (HABs)

HABs represent the most notorious marine hazard to man and animal alike. It is estimated that over 60,000 individual cases and clusters of human intoxication occur annually in the US alone. Worldwide, harmful algal blooms cause a variety of acute, sub-acute, and chronic diseases in humans, as well as in other mammals, fish, and birds. Health effects in humans range from acute neurotoxic disorders (such as polyether seafood poisonings, e.g., neurotoxic shellfish poisoning and ciguatera fish poisoning) to chronic and persistent diseases (such as amnesic shellfish poisoning and chronic liver disease caused by the cyanobacterial toxins, the microcystins).

Disease caused by exposure to environmental chemicals produced by harmful algal bloom organisms initiates with consumption of contaminated seafood or the inhalation of toxins entrapped in sea spray. The oral route of intoxication is by far the better understood and more commonly recognized, and coastal states all have public health surveillance and monitoring systems in place to prevent human intoxications. However, exposure to aerosolized particles in Florida red tide (and putative *Pfiesteria* outbreaks) is not uncommon and is an intoxication route much more difficult to quantify or control. It is conjectured, but unproven, that the mechanism of intoxication and death is the same for man and animal.

While it is readily recognized that HABs produce toxins that affect living systems, there are major gaps in our knowledge. Areas requiring further research include:

- *Biosynthesis and function*: New toxin types such as the spirulides and cylindrospermopsin expand the number of distinct chemical entities. A complete matrix description of the families and classes of organisms that produce HABs is required. A description of the biochemical pathway(s) by which distinct organisms produce toxins is necessary. What is the nature of the ecology, genetics, and enzymology that confer toxigenicity? What is the precise role of such compounds in aquatic microalgae? Can their synthesis be regulated?
- *Extrapolated materials*: In order to precisely develop analytical detection methods and for all types of toxicological and transport studies, specifically labeled toxin derivatives are necessary. Designer toxins, developed through organic manipulation, genetic manipulation of HAB genomes, and metabolic manipulation through the use of designer substrates, hold potential for producing many new tools for research and diagnostic uses.
- *Exposure and effect assessment*: Toxins produce their effects at concentrations that approach limits of detection in many cases. Principal in exposure assessment studies are developing a concept of what it is that should be measured. Biomarkers of exposure are crucial for diagnosis, treatment, prognosis, and epidemiological evaluation of these toxins and their possible human health effects. In general, the epidemiology of the harmful algal blooms has been poorly described, often dependent on case reports and case series associated with specific outbreaks.
- *Prevention and Control*: Cleanup and remediation require intervention in our foods, water, and air. What is the natural progression of HAB events? Do they exhibit toxic potential at all stages? Are there environmental parameters that can be altered to modulate HAB initiation, maintenance, or dissolution? Are HAB events predictable and preventable? Can oceanographic and biomedical technologies be coupled to produce smart sensors that detect developing blooms, together with relevant ecological and physical data?

Studying marine organisms for sources of new drugs

Terrestrial plants, animals, and microbes are a source for more than half of the medicinal drugs on the market today. Although marine biodiversity is immense (32 of 34 phyla), technical difficulties and lack of knowledge of the marine environment have prevented scientists and researchers from more fully exploring the use of marine life and its derivatives to prevent and treat human disease. Multidisciplinary research is required to investigate marine species that potentially are a source for new drugs and to identify the marine environment that will support cultivation of these organisms. Such research must extend beyond the discovery of anti-cancer drugs. Areas requiring further investigation are:

- *Marine biodiversity and organisms*: Multidisciplinary research and training are needed to increase our knowledge of marine organisms and their value for new therapies. Microorganisms pose a particular challenge because of the difficulty in classifying and culturing them; at the same time, they represent a novel resource for discovery of pharmaceuticals. New applications of molecular genetics should be conducted in order to isolate biosynthetic genes from these organisms and to express these pathways in expression hosts for production of marine pharmaceuticals.
- *Molecular mechanisms of natural marine toxins*: By understanding molecular mechanisms of toxins, researchers will be better equipped to develop drugs that can block the biological activity of a toxin. New methods for detecting toxins in seafood can also be developed. Lastly, this information can provide researchers with new tools for understanding the biochemistry of the nervous system.
- *Techniques for culturing marine organisms*: Although marine biodiversity is immense, the availability of many organisms is not. New techniques for culturing such organisms are needed to fully understand their therapeutic potential. Although several techniques exist (e.g. aquaculture, cell culture, and microbial fermentation), there remain many questions about their ability to produce organisms that will have the same potential to yield biologically useful compounds and pharmaceuticals.

Reducing morbidity due to water- and vector-borne diseases

It has been estimated that human pathogens in the marine environment lead to significant health problems and annual losses of billions of dollars of income worldwide. The two main routes of human exposure to marine water-borne disease are (1) eating fish, especially shellfish, and (2) recreational contact, such as swimming or surfing. Types of pathogens include bacteria, viruses, and protists. Bacteria include native marine organisms (e.g. *Vibrio vulnificus*, *V. parahaemolyticus*), but mostly those originating from humans and terrestrial animals. Because viruses tend to have a limited host range, human pathogenic viruses in seawater most probably come from human sources (primarily via fecal transmission, but possibly blood-borne via blood in the wastewater stream). Protists can include native forms, such as toxin-producing dinoflagellates (discussed under the topic of harmful algal blooms) and possibly also others like *Cryptosporidium* and *Giardia*.

Human- and terrestrial animal-derived pathogens in seawater primarily enter the sea from sewage and runoff, including agricultural runoff, although it is also possible to have transmission between swimmers (particularly at very crowded beaches). Sewage (usually treated in developed countries) enters the ocean via submerged outfalls and sometimes rivers, while runoff is rarely treated and enters via rivers or directly onto the shore. Raw sewage can enter the sea from runoff

via leaking and aging sewers, improperly functioning septic systems, or locations where sewage treatment is lacking or inadequate. We know relatively little about the fates of most pathogens in marine environments.

Survival and persistence of various pathogens is strongly influenced by environmental conditions. Global change has the potential to alter significantly the existing patterns. For example, pathogens now largely limited to tropical areas are likely to move pole-ward under a general warming scenario. Therefore, the current pathogen types found at coastal U.S. cities may change in the near future, and organisms like pathogenic *Vibrio cholerae* may become a problem. It is also important to realize that microorganisms undergo gene transfer, including genes coding for virulence factors and antibiotic resistance. Therefore, relatively benign forms may become pathogenic and/or resistant to antibiotics, and pathogenic forms may become more prevalent. As we experience increased human population pressure in coastal areas and changes in environmental conditions, this may lead to an increased importance of marine-borne pathogens. Within this field, additional studies may address:

- *Detection and quantification*: New tests are needed to detect waterborne pathogens more quickly and efficiently. These tests should also be more affordable and require less sample volume. Environmental monitoring for pathogens should be coordinated with targeted epidemiological investigations to identify populations at risk. Moreover, interdisciplinary research is needed to examine the potential for global climate change to affect the spread of human diseases. For example, the cause and effect relationships among sea surface temperature, nutrients, plankton, *Vibrio cholerae*, disease incidence, and climate variability should be studied.
- *Pathogenicity*: Use of genomics and proteomics will lead to better understanding of pathogenicity and survival of marine-borne pathogens and to development of genetic and immunological detection approaches. Characterization of factors controlling pathogen survival in seawater, and spatial/temporal patterns of dispersal, transport, and partitioning into suspended particles and sediments will enhance our understanding of the fates of pathogens released into the sea.
- *Prevention*: Epidemiological studies are needed to evaluate risks of various pathogens. Rapid, accurate, and affordable tests, requiring relatively small sample volumes, are needed to detect and quantify the various pathogens in water and shellfish. Animal viruses should be surveyed for relatives of human marine-borne pathogens, to avoid false positives in genetic or immunological tests. Alternative wastewater, runoff treatment, or disinfection methods can be evaluated under realistic conditions. Nearshore physical and geological oceanography can be applied to study the transport of pathogens where human exposure occurs, for evaluating problems with existing systems, and to assist in siting and design of new or replacement sewage and runoff outfalls.

Beyond these three primary research foci, other areas of research may include:

- *Gathering data and conducting research to predict and prevent marine-related public health disasters*. In addition to the health disasters brought about by El Niño, devastating hurricanes and other weather and climate phenomena linked to the oceans, many public health officials are concerned that high water temperatures brought about by global warming will result in increased populations of mosquitoes and other disease-carrying organisms which in turn could give a rise to an increased incidence of malaria and

dengue fever. Ocean-related data on temperature, tropical storms, rainfall and droughts should be examined regularly and compared with comprehensive health statistics on the location, frequency and dates of disease outbreaks, to identify connections between illnesses and environmental factors.

- *Understanding risk associated with ingestion of contaminated seafood.* Growing demand for seafood and expansion of ocean-going transport have increased the potential for human exposure to infectious and toxic agents. The risk to humans who ingest large amounts of seafood needs to be determined as well as identifying the point or source of contamination. Exposure data via the ingestion of persistent organic pollutants (such as DDT and PCBs) and metals (such as mercury and cadmium) should be evaluated and put in context of seafood consumption. Also accurate, cost-effective methods should be developed for identifying and monitoring toxins in seafood.
- *Using new technologies to help reduce human health risks.* Advanced sensors should be put in place to monitor marine conditions and water quality. For example, more sensitive and specific tests are needed to detect pathogens introduced into oceans through runoff from sewage, rivers and streams. In addition, development and use of miniature instruments that can be used by fishermen and lifeguards would assist in understanding water conditions and human health effects.

Goal

In collaboration with the National Science Foundation (NSF), Division of Ocean Science, NIEHS seeks to develop an inter-agency, multidisciplinary research and prevention center program focused on detecting potential marine-based contaminants, preventing associated illness, and developing products from the ocean that will enhance human well-being.

Description of Centers in Oceans and Human Health (COHH)

The COHH are envisioned as multidisciplinary research programs in the diverse areas of oceanography, geology, climatology, ecology, biomedical science, and computational biology. Such centers would provide for a national network of investigators and foster an interconnected research approach dedicated to understanding the complexities of linking oceans and human health.

Each center may be developed around a central research theme and be comprised of multiple research projects, facility cores, and a translational research component. The central focus or theme for each program will be supported by fundamental, hypothesis-driven research projects that are comprised of both biological and physical sciences. It will be important for centers to explore diverse ecosystems and their unique exposure pathways (e.g., polar regions, urban harbors, small tropical islands). Facility cores will provide technical support to research projects and promote interactions among investigators participating in the program. It is envisioned that development and validation of sensors (both oceanographic and biological) will be a key function of service cores within centers. Data generated from center research efforts will require establishment of a translational research core, which will provide support for collection of sophisticated data and information transfer and ensure that research findings are communicated to the general public, scientists, and policymakers.

Proposed Plan

NIEHS recognizes that this program will benefit from partnership with one or more other federal agencies. Presently, NIEHS plans to partner with NSF, Ocean Sciences Division, as it has expertise in physical sciences that compliments NIEHS' expertise in health sciences. This partnership will take place at both scientific program management and fiscal levels, such as the partnership NIEHS has developed with EPA for the Centers for Children's Environmental Health and Disease Prevention Research (<http://inside-www.niehs.nih.gov/translate/children/children.htm>).

Other potential partners include National Oceanic and Atmospheric Administration (NOAA) and National Aeronautics and Space Administration (NASA).