FOGARTY INTERNATIONAL CENTER
STRATEGIC PLAN: FISCAL YEARS 2000-2003

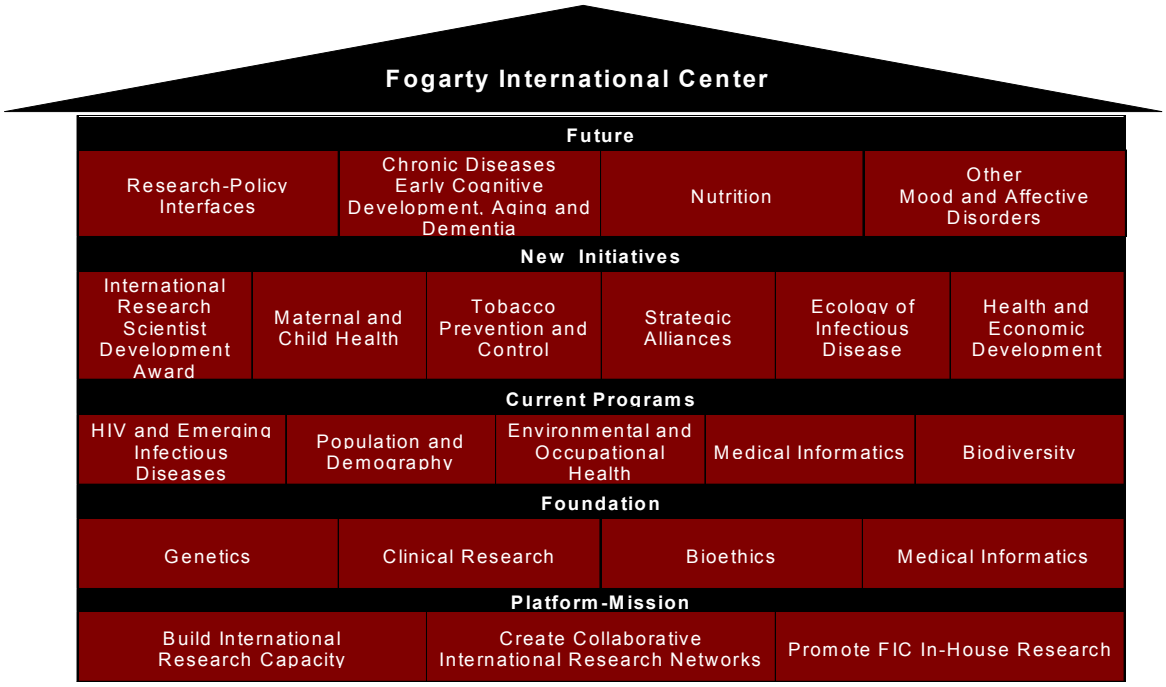
REDUCING DISPARITIES IN GLOBAL HEALTH

But my final argument, in my last ditch, is the simplest . . . We have an obligation to assure something more like fairness and equity in human health. We do not have a choice, unless we plan to give up being human. The idea that all men and women are brothers and sisters is not a transient cultural notion . . . It is a biological imperative.
Lewis Thomas, The Fragile Species

Contents

Panels

- *FIC Mission Statement*
- *Landmark Discoveries Derived From International Cooperation in Biomedical Sciences*
- *FIC Research and Training Initiatives: Program Attributes*
- *Components of an Effective Research Support System for International Health*
- *Evaluating International Benefits of FIC Investment*
- *Addressing Global Health Needs*
- *AIDS International Research and Training Program*
- *Leadership in Global Health: Malaria*
- *Factors Contributing to Disease Re-emergence and Examples of Associated Infections*
- *FIC Research and Training Opportunities*



Building The Fogarty International Center of The Twenty-first Century.
Leadership, innovation and collaboration in research, research training and policy internationally.

I. INTRODUCTION

In describing the international programs of the Fogarty International Center (FIC), what is past is indeed prologue. A founding mandate of the first Laboratory of Hygiene, the Federal predecessor to NIH established in 1887, was to study diseases that were global in origin. Its first Director, Joseph Kinyoun, trained in Europe in the laboratories of Robert Koch and Louis Pasteur and learned bacterial isolation techniques that enabled him to make the first bacteriologically proven diagnosis of cholera in the Western hemisphere and take action to prevent its introduction into the United States. That early landmark presaged two operating precepts for the NIH: that basic science yields practical benefits—Kinyoun's discovery helped establish the conceptual foundation of sanitation law-- and that international research often may accelerate discovery. This second precept was codified in law when the modern NIH was authorized to extend its extramural program overseas.

The historic social contract that formed between the government and medical research institutions in the United States and elsewhere became the model for establishing medical research councils throughout Europe. This entrepreneurial approach has encouraged a dynamic exchange of concepts, methods, data, and scientific personnel among laboratories worldwide. A prominent example is the discovery of the helical structure of DNA, which resulted from the convergence of two paths of discovery. British scientists endeavored to understand the three-dimensional structure of biomedical molecules, while their U.S. colleagues elucidated the mechanisms and chemistry of heredity. Through a series of landmark discoveries made possible through international collaboration, molecular biology emerged in two decades from an embryonic discipline to an applied science with profound implications for health and agriculture.

FIC Mission Statement

To mobilize scientific resources to reduce global health disparities and to prepare the current and future generation of scientists to meet global health needs

The Fogarty International Center (FIC), which celebrates its thirty-third year in 2000, embodies the historic mandate of the Laboratory of Hygiene, science for global health. The Center is the mainstay at the NIH for the promotion of global scientific cooperation through the support of grant and fellowship awards to U.S. institutions to extend the geographic scope of research and training. FIC supports over one hundred U.S. institutions, which collaborate with over ninety nations on studies ranging from the genetic basis of disease and the fundamental properties of the cell, to nutritional interventions to improve maternal health, or strategies to prevent transmission of HIV. These efforts are multidisciplinary, embracing clinical, epidemiological, basic biomedical and behavioral research. And, as we look ahead, FIC will increasingly be directly involved in cross-cutting research through both extramural and intramural research programs.

The FIC pursues three core objectives. The first is to accelerate the pace of discovery and application by enabling scientists worldwide to share conceptual insights, analytic methods, data sets, patient cohorts or special environments. The second is to engage and assist U.S. scientists to address scientific challenges related to global health. And the third is to help to develop a cadre of highly capable young foreign investigators positioned to cooperate with US scientists and conduct independent research in areas of the world that, due to geography, genetics, or disease burdens, provide unique opportunities to understand disease pathogenesis, anticipate disease trends, or develop interventions. This has been the conceptual basis for programs related to HIV and emerging infectious diseases, population and demographic

science, maternal and child health, environmental and occupational health, applied medical informatics, drug discovery through responsible "bioprospecting" and more fundamental studies on the cellular, molecular and biochemical basis of health and disease. A list of current programs appears in Panel 1, constituting the program base on which the scientific plan for fiscal years 2000-2003 has been constructed.

The Status of Global Health

As we approach the new millennium, prominent challenges confront global health. The world's poorest regions still endure a heavy and largely avoidable toll of premature death due to childhood infections, malnutrition and poor reproductive health. These conditions, characterized as our "unfinished agenda," account for over one-third of the entire global burden of disease. Alarmingly, malaria alone kills one person every twelve seconds, most likely a child under five years. Of the 16,000 new HIV infections each day, ninety percent occur in low- and middle-income nations, mainly young adults in their most economically productive phase of life. Moreover, as lifestyles and life expectancy begin to shift toward patterns of the industrialized world, many low- and middle-income nations will experience an increased incidence of chronic conditions such as tobacco-related cancers, cardiovascular diseases, diabetes and mental health disorders.

Two trends converge to present a new category of health threats due to communicable diseases for all populations. The first is the unregulated, widespread use and misuse of antimicrobial drugs, which has lead to the emergence and global spread of drug-resistant pathogens. The second is demographic and technologic change, which have set the stage for rapid spread of microbial threats to health, including drug-resistant pathogens, and their introduction into the United States. The global nature of this threat is exemplified by the observation that following the first cases of vancomycin resistant enterococci identified in Japan similar cases appeared in the United States within months. This drug resistance has now spread to other bacteria, such as *Staphylococcus aureus*, a common cause of post-surgical infections and other serious life-threatening acute illnesses.

The trends described are exacerbated by logarithmic increments in the rate of growth of the world's population. According to United Nations projections, global population will stabilize at between eight and fourteen billion people in the next century. More than ninety percent of the increase will occur in the poorest countries, largely in the world's already overpopulated cities. The public health outcomes of this demographic pressure have been well-described by present-day Malthusians. Major unintended changes already are occurring in the atmosphere, soil, water, among plants and animals, and in the relationship among all of these. To cite one disturbing projection, hydrologists estimate that based on current demographic trajectories, within the next twenty-five years African countries will no longer be able to meet water needs from rivers and local aquifers. The number of Africans who already are "food insecure" exceeds 100 million, a predicament that will surely worsen as continued population growth outstrips available resources and increasing investments are required to continue current gains in global food production. Thus, it is estimated that a five-fold increase in energy use will be required to bring food consumption in low- and middle-income nations to the levels of industrialized countries by 2025. The state of our global village is precarious at a time of increasing promise of science to address and alleviate these disparities.

From Molecular Medicine to Global Health

International research in biomedicine is essential for guiding strategic action to blunt these trends. By 1900 scientists had demonstrated the microbial origins of disease, a discovery that transformed our understanding and treatment of infectious disease, and had already led to the development of vaccines for diphtheria and tetanus based on the new sciences of microbiology and immunology. Today, we are at a similar watershed. Whether encompassing the study of disease at the level of cells and molecules or the maintenance of health in the community, the biomedical research enterprise has entered perhaps the most rewarding era in its history. New research tools to examine biologically critical genes and the molecules they encode are increasingly employed in all areas of clinical and epidemiological investigation for diagnosis, prognosis, and the identification of new targets for therapeutic drug development. Advances in high performance computing and communications now allow scientists to collaborate, analyze data and test models from remote locations creating new interdisciplinary interfaces for scientific discovery. New, highly sensitive and specific assays are enabling scientists to detect biological changes at the molecular, genetic, biochemical, and cellular levels, better quantify risk factors and assess the effectiveness of interventions. If we harness these global opportunities, the prospect of new discoveries through international population-based research is especially promising.

At the edge of the 21st century, disciplinary barriers between fundamental and more applied science have eroded. In biomedicine, the linear model of scientific pursuit, where basic studies lead to more applied research is being supplanted by a true reciprocity between clinical and basic science. International population-based studies are yielding insights that not only lead to new medical applications, but increase fundamental understanding of disease pathogenesis. An exciting example is HIV research, where the discovery of the role of chemokines and their receptors in HIV infectivity resulted from observational studies of highly exposed yet persistently uninfected HIV-positive volunteers in the U.S. Western Europe and Sub-Saharan Africa who did not progress to clinical disease. This finding may result in new methods of inhibiting the virus from penetrating and multiplying within target cells. Multinational studies also hold unique advantages in epidemiological research, exploiting the genetic, cultural, dietary and social differences among populations to understand disease determinants. For instance, our understanding of dietary risk factors for cardiovascular diseases was strengthened through longitudinal studies of cardiovascular disease morbidity and mortality in Asian populations who migrated to the United States and altered their intake of dietary fat.

Landmark discoveries derived from international cooperation in biomedical sciences

Discovery	**Nature of international cooperation**
Recombinant tissue plasminogen (tPA) to limit muscle damage in heart-attack victims	Collaboration between University of Louvain, Belgium, and Washington University, USA; clinical trials funded by Genentech
Oral rehydration therapy as low-cost, highly effective treatment for severe diarrhoea	Developed at Pakistan-SEATO medical research laboratory [now the International Center for Diarrhoeal Disease Research (ICDDR,B, Bangladesh)] with major support from the NIH
Monoclonal antibodies yielding reagents of unprecedented specificity in all aspects of biological science and increasingly of value as therapeutic agents	Initial collaboration between Cambridge University, UK, and Salk Institute, USA
Vaccines	
Oral polio (Sabin)	First tested in former Soviet Union in more than 15 million children*
Hepatitis virus	First non-serum hepatitis-B vaccine field tested in China and Senegal; one of hepatitis-A vaccines field tested in Thailand
	Discovery of an antigen in Australian aboriginal blood samples that detected the presence of hepatitis B in the blood and led to the development of screening test to prevent hepatitis B infection through transfusion.
Cholera	Whole-cell vaccine licensed for use in USA developed in Sweden and tested at ICDDR.B
Identification of genetic mutation that causes Huntington's chorea	Studies of large kindred of Huntington's patients living in Venezuela
Establishment of firm links between DNA viruses and cancer, and confirmations of risk of heterosexual and perinatal transmission of HIV-1	Cooperation with scientists at University of Makerere and University of Ibadan, Nigeria, and in other sub-Saharan African sites helped confirm causal link between Epstein-Barr virus and Burkitt's lymphoma, early evidence of role of DNA virus in cancer; range of infectious agents now associated with human cancers, partly owing to international collaborative studies
Development of novel therapeutics through study of indigenous biological resources	Discovery of anti-cancer properties of plant indigenous to Madagascar—rosy periwinkle; subsequently identified as two alkaloids that constitute the drugs vinblastine and vincristine, employed in multi-drug regimens for Hodgkin's disease and acute lymphocytic leukaemia
	Discovery of important class of antihypertensive agents—ACE inhibitors—from extracts of plants collected in Ghana, Malaysia, and Costa Rica

The rationale for US engagement in global health extends beyond humanitarian imperatives. HIV and other pandemics demonstrate that health conditions are not demarcated by national borders. Disadvantaged groups in the United States share similar health risks with resource poor nations, such as tuberculosis, micronutrient deficiencies and perinatal infections. Thus,

there are lessons to be learned domestically from research conducted in low- and middle-income nations. Recent careful collaborative studies conducted in Tanzania demonstrate that unless drug treatment for tuberculosis is properly supervised tuberculosis rapidly becomes resistant to available drugs. This finding has been applied in community health programs in metropolitan New York and other cities where tuberculosis is a public health problem.
In its recent report, *America's Vital Interest in Global Health*, the Institute of Medicine noted the economic benefits that accrue through increased engagement in global health. The global health market represents $1.7 trillion, the equivalent of 8 percent of the world's economic output. In 1992 (latest data available) the pharmaceutical and medical device market represented around $300 billion, $44 million of which constituted exports to low- and middle-income nations. Despite U.S. prominence in the creation of new drugs and medical devices as measured by percentage of world patents, its global market share of exports to low- and middle-income nations is less than15 percent. This is due to a combination of both historic and economic circumstances. However, international scientific cooperation is one means to help rectify this "market failure." Increased cooperation in the biomedical sciences is a pathway of access to emerging and developing markets. The benefits are both economic and humanitarian: increased U.S. access to these markets will allow citizens of low- and middle-income nations to more easily procure affordable drugs.

The Fogarty International Center is poised to take a leadership role, together with the Institutes and Centers at NIH, in forging the global alliances and cooperation needed to combat disease and advance health for all the peoples of this planet.

FIC Research and Training Initiatives
Program Attributes

- Scientific and training programs will address widening disparities in global health that require cooperation at a strategic level.
- Activities will be designed to complement, and not compete or overlap with NIH categorical institutes, each of which supports international research projects through extramural programs.
- Emphasis will be placed on scientific training and career development for young investigators in the U.S. and scientists from low- and middle-income nations, a need not addressed systematically through the training programs of the categorical institutes (due in part to eligibility restrictions on the National Research Service Awards—NIH's dedicated mechanism for training).
- Programs will support a broad range of disciplines in a given area to provide applicants with a broad creative margin and to pursue an integrated approach.
- Grant competition largely will be limited to scientists who already have been awarded an NIH research project grant to ensure a strong base on which to launch an international research and training program.

Strategic Alliances and Cross-Sectoral Partnerships

A leading historian has noted that a principal contribution of the United States to science in the 20th century has been its entrepreneurial sprit, which is invested in the working principle of investigator-initiated research. In an analogous sense, research administrators must become venture capitalists in the biomedical research enterprise, structuring investment to advance long-term, strategic goals rather than near-term performance. Projecting from its current level of expenditure, the FIC will spend more than $700 million over the next 10 years to advance international cooperation. To use these resources in the most efficient and effective manner,

the FIC will need to maintain an international perspective that encompasses both the categorical interests of the NIH institutes and broader strategic needs. Based on shared health interests and shared financial constraints, alliances between and among the NIH, foreign medical research councils, and other international sources of biomedical support will become important modes in planning and conducting international programs. Effective "intelligence systems" related to the research priorities and strategies of other funding bodies will be useful in identifying potential alliances. Strategic partnerships are particularly needed in areas where respective missions cannot be accomplished in isolation for reasons of economy, synergy, or both. Although international cooperation in the biomedical sciences occurs most effectively at the scientist-to-scientist level, there are circumstances when it may be constructive for agencies and organizations to work in concert to facilitate these arrangements. These include:

- training and career development;

- shared resources such as tissue banks, cell lines, primate centers, cDNA, probe and YAC libraries, databases, patient cohorts, and large instruments (e.g., synchrotrons);

- coordination at a strategic level, such as genome or brain mapping, or cross-cultural population-based studies; and

- issues of general policy, such as bioethics and intellectual property considerations.

Collaborative arrangements with external organizations should incorporate the working principles of NIH: co-sponsored programs should be based on objective assessments of medical and public health needs, the state of scientific knowledge in a given field, and technical advances that make feasible new experiments; emphasis should be placed on investigator-initiated science; and all projects should be subject to rigorous peer review. The process and procedures for collaborative funding require clear definitions of shared obligations and expectations. As a result, a model framework will be developed that considers such issues as equity, shared priorities, and mutual benefit, the application review process, funding criteria, out-year commitments, confidentiality and conflict of interest, and intellectual property rights.

In contemplating new partnerships, several trends merit examination with regards to health resource allocation. Constraints in funding within selected organizations that have traditionally supported international health research, including the World Health Organization, other specialized United Nation's agencies, and the United States Agency for International Development, has required these organizations to realign funding priorities. At the same time, development banks and private foundations have recognized the relationship between health and development and related training needs that can be met through new or redirected investments. These shifting trends require FIC and its sister institutes at NIH to gain a more nuanced understanding of priorities and incentive structures that determine the flow of resources into international health fields from governmental, multilateral, and non-governmental organizations—and to establish more systematic working arrangements with these institutions. A leading outcome of this effort would be to ***assimilate biomedical and behavioral research and training into disease control and prevention, health promotion, and clinical services,***

and to more fully integrate biomedical and behavioral research into development and health assistance programs.

An overarching objective to be achieved through strategic alliances is to increase research capabilities in low- and middle- income nations, both to build an indigenous research capacity and more effectively meet global health challenges through international collaborations. One instructive precedent may exist in the field of international agriculture research. Over past decades, agricultural science has been a major beneficiary of a consortium known as the Consultative Group on International Agricultural Research (CGIAR). Encouraged by the initial success of the Ford and Rockefeller Foundations in agricultural science, CGIAR was established as an international council of international development organizations to influence investment decisions through periodic evaluations of research needs. Through judicious planning, this consortium has supported research centers which among other accomplishments realized genetic improvements in cultivars and served as a distribution point for germ plasm for breeding programs throughout the developing world. Research centers affiliated with CGIAR function in a manner similar to U.S. land grant institutions, directed to support the application of technology with linkages to development agencies and national governments, academic research centers and extension services. Based on this model, the FIC has identified organizational attributes that enhance the capabilities of research institutions in low- and middle-income nations to contribute the global health research enterprise. In the planning and development of scientific programs outlined in this document, FIC will promote these conditions where feasible.

Investments to build research capacity in low- and middle-income nations directly influence our domestic capacity to develop an adequately trained cadre of international health specialists. In order to prepare the future generation of US specialists in fields such as parasitology, infectious disease immunology and nutrition, genetics, environment and health and chronic diseases, scientists must be linked to centers of research excellence in regions with endemic burdens early and continually throughout their career. These centers must possess the laboratory infrastructure, clinical and field capabilities required for a comprehensive study of disease etiology, pathogenesis, prevention and control. US supported research laboratories overseas have played an historic role in the discovery and monitoring of infectious disease, the understanding of the systemic effects of micronutrient deficiencies and other global health problems and have provided a locus for the training of US professionals. Examples include the Middle American and Pacific Research Units, the South East Asia Treaty Organization (SEATO) Medical Research Laboratory in Bangkok, the U.S. Army and Navy laboratories around the world, and the Rockefeller Foundation Virus program. However, over the past several decades the number of these facilities has declined. Their loss has left a gap in our capacity to train US scientists in global health. However, strategic investments by other agencies, domestic and international, offer the promise of enhanced training and research opportunities if they are linked and coordinated into a collaborating network promoting mutual benefits.

Components of an Effective Research Support System for International Health:

Attributes of Centers of Excellence in Low- and Middle-Income Nations

- Capacity to train large numbers of individuals from whom subsequent leaders emerge
- Integration of laboratory and field investigation
- Interdisciplinary competence: capacity to assess multiple factors on incidence, severity and outcome of endemic problems

- Monitoring and evaluation capacity
- Stable core funding for laboratory and field investigation
- Clinical facilities
- Capacity to secure significant element of competitive funding
- "Internationalization:" Ability to recruit established scientists for extended residence
- Collaboration with multiple institutions, including regional counterparts
- Ability to exploit communications and computational technologies (e.g. e-mail, access to databanks and analytic tools; electronic peer-review)
- Autonomous management
- Statistical and data management support
- Administrative capabilities (e.g., grants and contract management)
- Mechanism to transfer research findings into local practice or linkage to national decision-makers
- Competence in data and safety monitoring
- Competence in ethics review
- Integration with local community (e.g., community advisory board)
- Administrative associations with international organizations (e.g. WHO collaborating Center)

Conceptual Framework of the FIC Plan

Long-range planning is a dynamic and prospective process. The FIC strategic plan is intended to present an analytic framework for the identification of scientific priorities and distribution of resources. It is not intended as a manual of operations, but rather a framework for decisions on program changes and redirections. These will be implemented through a variety of mechanisms to include program recompetitions, program initiatives, workshops and multi-agency consortia and consultations, internal and contracted studies. The plan also is conceived as a working document malleable to changing global health needs and unanticipated opportunities that may emerge through technical innovation or other developments.

The principal advisory arm for FIC planning is its chartered Advisory Board, augmented by *ad hoc* expert panels and public councils convened under the aegis of the Board. In support of planning initiatives outlined in this report, sub-committees of the FIC Advisory Board will be established in selected areas (advanced studies, population biology).

The strategic planning exercise is the prime management tool to guide both program operations and organizational structure at FIC. A series of working tenets serve as conceptual guide. First, the FIC actively involves the broader NIH community and Federal government in program planning to deepen the potential pool of resources and expertise. For example, technical advisory groups are formed with other agencies to discuss prospective FIC initiatives and directions prior to the formulation of program plans. Second, in support of the planning process FIC continually assesses trends that influence international programs in biomedicine, ranging from changes in disease epidemiology to new intellectual property laws. A key feature has been participation in domestic and international policy fora and creative use of web-based interactive databases to solicit perspectives from foreign experts and institutions. The Director is serving in various capacities at WHO, with the Committee on Global Health of the IOM, also with policy boards at interantional Foundations such as the Wellcome Trust. Third, the Center is establishing short- and longer-term program objectives as a means of focusing resources and staff efforts. Rather than a system of strictly quantitative metrics, often unfeasible in a research environment which relies on the creative-initiative of the individual investigator, FIC will adopt qualitative measures of outcome, such as success in engaging the participation of external agencies in FIC initiatives. Fourth, the Center will establish a system of performance measures at the organizational level to inform day-to-day management. For example, by setting a performance goal that international research collaborations should continue beyond the duration of an FIC-sponsored grant award, managers will target prospective sources of "spin-off" or

external support early in the duration of the grant and assist FIC-supported trainees in grantsmanship skills. And finally, the Center will engage in a series of outreach activities to assist the public to comprehend the interdependent nature of global health. Here, the Center's aspiration is to create a more informed "constituency" for public investment in international health research.

Evaluating International Benefits of FIC Investment

The Causal Chain from Program Inception to Results

In constructing evaluation plans for FIC programs, the following components will be assessed through a system of metrics individual to the given program.

RESOURCE INPUTS

FIC's level of fiscal and staff investment in a given program.

PROGRAM OUTPUTS

The immediate, observable products of research activities on the individual and/or institution, such as publications or patent submissions, citations in Investigational New Drug Applications, degrees conferred, resulting appointments.

PROGRAM OUTCOMES

The longer-term results for which a program is designed to contribute, such as strengthened research capacity within the US and foreign laboratory, effective transfer of scientific principles and methods, success in obtaining further international support.

PROGRAM IMPACTS

The total consequences of the program, including unanticipated benefits or unmet results, such as influence of research activities on clinical and public health practice or health policy, success in establishing a sustainable career structure.

In developing a planning framework for the near-midterm, FIC has endeavored to address a series of critical questions on international program and policy needs, based on trends in biology, medicine and global disease burdens. Prominent among these are the following:

- *What are the implications for international health as we make the transition from structural to functional genomics? What should FIC be doing now to lay the groundwork for research to comprehend gene and environmental interactions as it relates to optimal health as well as chronic and infectious diseases?*

- *What is needed to lay the groundwork for the development and testing of vaccines that require testing in tropical/sub-tropical sites due to epidemiological characteristics of certain disease burdens such as malaria and microbial diarrhea?*

- *What is required to graft effectively an international research agenda on to current global efforts in microbial surveillance, including identification of reservoirs of drug resistance genes and the mechanisms governing horizontal transfer and spread? What is the feasibility of a research "sentinel system" to develop data and predictive models at international sites and what are its components?*

- *Given its complex determinants, what are the evolving research strategies to stabilize population growth which FIC should consider? Does this suggest a broadened FIC role in the social and economic sciences?*

- *What should be the components of a "prevention science agenda" for HIV in low- and middle-income nations in light of current projections for an effective HIV vaccine?*

- *What is an appropriate FIC role in preventing and containing "post-transition" diseases in low- and middle-income nations, and what are leading priorities and scientific approaches?*

- *How does one alter career incentive structures to encourage more domestic scientists to train or pursue studies at foreign sites—and increase the cadre of Americans engaged in international health research? Is it feasible to consider an "international health corps" of scientists analogous to the (now defunct) PHS physician corps which committed to serving underprivileged communities?*

- *What is an appropriate public role in engaging more industrial R&D toward products relevant to low- and middle-income nations, such as vaccines and microbicides?*

- *What international science R & D models are there that may be extended to other disciplines such as biomedical research? For example, what are the lessons that may be extrapolated from agricultural science to improve the research support system for international health?*

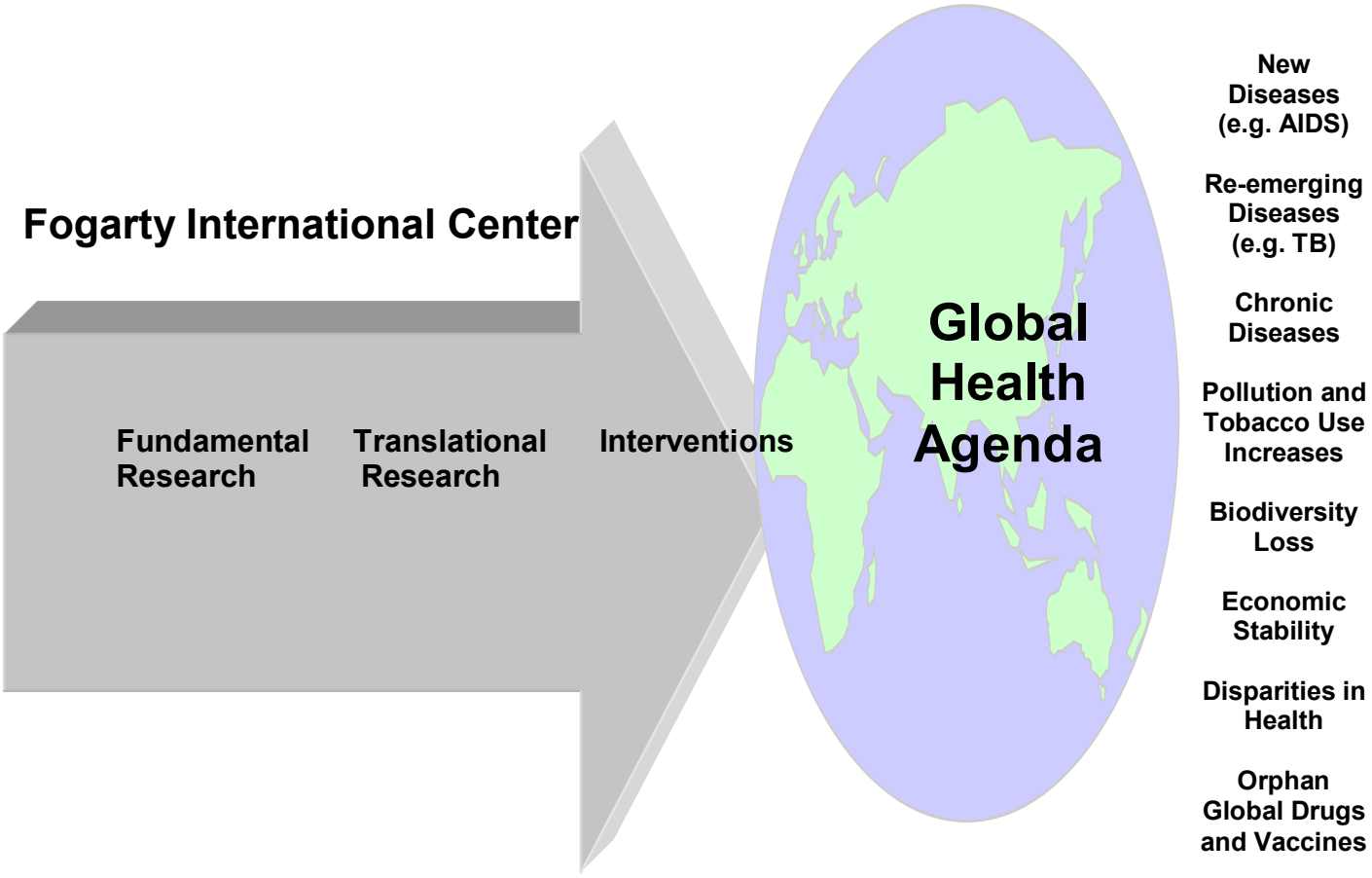
- *How might advances in information technologies be exploited in the context of clinical practice, distance learning, disaster relief, and the construction of scientific "collaboratories" (interactive research networks), especially given the variable state of telecommunications infrastructure throughout the developing world?*

- *What are the scientific "synergisms" or transdisciplinary fields among our current programs that could be developed? For example, should efforts be made to link selective disciplinary studies into multidisciplinary centers of excellence?*

Organization of Strategic Plan

The strategic plan that follows is organized around categorical challenges in global health research, such as maternal and child health and emerging infectious diseases. In each section, a brief precis is first presented on current and prospective lines of scientific investigation, followed by an outline of FIC program development goals and related training needs.

ADDRESSING GLOBAL HEALTH NEEDS



II. THE UNFINISHED AGENDA: IMPROVING CHILD AND MATERNAL HEALTH

Population Growth

A key determinant in coping with the global disease burden is our capacity to stabilize population growth. Strategies to reduce fertility rates present perhaps the most complex and multifactorial challenge facing global health. Population increases are estimated to be a prime cause of both poverty and malnutrition; yet inversely, the deteriorating health and economic status of many low-income nations may result in higher fertility rates. Sustained decreases in fertility rates ultimately may depend upon economic progress, the development of a more literate and numerate society, and improvements in the status of women. Perhaps the most direct means to reduce unwanted pregnancies is to strengthen family planning programs. Regression analyses indicate that organized family planning programs have accounted for 40 to 50 percent of global fertility decreases to date. Although family planning efforts in low- and middle-income nations have been substantial through organizations such as the International Planned Parenthood Federation and UN Population Fund, religious beliefs and cultural practices often discourage the use of contraceptives. Many women in low- and middle-income nations lack the autonomy to make use of contraceptive devices, which has been a determinant of fertility rates as well as prevalence rates for HIV and other sexually-transmitted diseases. Efforts to create a broader range of sage and reversible contraceptive methods—both temporary and long-acting—must be complemented by research on cultural values and beliefs which influence the use and choice of contraceptive methods.

The current FIC program in this area is the *International Training and Research Program in Population and Health*, co-sponsored by the National Institute of Child Health and Human Development (NICHD). The program enables US institutions to pursue a range of activities with low- and middle-income nations, including field and laboratory-based studies, training fellowships and regional workshops.

Program Development Goals and Related Training Needs

- *Pursue new and improved contraceptive devices and agents, including natural or synthetic agents, products to reduce transmission of sexually-transmitted diseases, new contraceptive devices and reversible sterilization techniques.*

- *Evaluate contraceptive and fertility-related drugs and products for safety and efficacy.*

- *Identify social and behavioral factors that influence population growth and change, including contraceptive use and choice and societal roles of women.*

- *Promote operational research related to family planning, migration and spatial distribution of population, family composition and parental roles, and population policies.*

Strategic Alliances:

- *Develop partnerships leading Non-Governmental organizations with programs in the population sciences and demograghy, such as the Population Council.*

Maternal and Child Health

Ultimately, the effectiveness of family planning is dependent on reduction in the continuing demand for large families. High death rates among children result in excess births to ensure that a desired number of children survive to adulthood. An extensive survey conducted in 27 developing nations in Africa, South America and Asia found no country with a desired family size of two; Africa reported the largest desired size, at six. This trend may slowly shift with gains in child survival and a transition from agrarian to industrial economies. Yet at present, in many developing countries child mortality rates exceed one in ten children. Improvements in prenatal health care through prevention research are essential to efforts to reach sustainable rates of population growth. The causes of early pregnancy loss include congenital anomalies, endocrine problems and infections. Congenital infections with cytomegalovirus, herpes simplex, syphilis, rubella and toxoplasmosis also cause fetal damage. Toxemia and high blood pressure are frequent complications of pregnancy and present significant maternal and perinatal risks. Moreover, efforts are required to increase the social and economic status of women and to encourage them to delay and to space childbearing. This may require increased insights into cultural values and mores through social research. In some low- and middle-income nations, rising levels of female education are strongly associated with declines in birthrates. Special efforts to recruit women in low- and middle-income nations into research and technical support fields is a modest but realizable strategy to increase the societal role of women.

In contemplating research needs related to the unfinished agenda of child and maternal health, it is notable that over seventy percent of child mortality in low- and middle-income nations is attributable to infectious diseases. Prominent among these are measles, malaria, microbial diarrhea and acute respiratory infections. Among other interventions to reduce this burden, the *WHO Ad Hoc Committee on Health Research Relating to Future Intervention Options* has advocated the strategy of grouping essential interventions into "packages" for the care of the sick child, immunization, family planning and obstetric services. These packages are perceived to increase care and efficiency by making best use of contact between health care workers and the community. For example, current immunization programs might be augmented to incorporate additional vaccines and micronutrients. A "sick child package" might integrate treatment of fever to prevent deaths from severe malaria, pneumonia and meningitis--conditions which share common risk factors. Health economists argue that these packaged interventions conceivably may avert one-third of the disease burden in low- and middle-income nations at modest cost (U.S. $12 per person/per year). Expertise and cross-sectoral coordination are required to develop, evaluate and refine these packages in local settings. In addition, research is required to determine which combinations of interventions achieve the greatest synergy of effect and health benefit, since all possible interventions can neither be packaged nor delivered together.

The current FIC program in this area is the *International Training and Research Program in Maternal and Child Health*, co-sponsored by the NICHD. The program enables US institutions to pursue a range of activities with low- and middle-income nations, including field and laboratory-based studies, training fellowships and regional workshops.

Program Development Goals and Related Training Needs

- *Develop and evaluate packages of services for antenatal care delivery and reduction of the burden of neonatal morbidity and mortality.*

- *Evaluate and refine the package for the Integrated Management of the Sick Child.*

- *Develop and test health promotion strategies during prenatal care that incorporate individual, community and social components.*

- *Develop and test model protocols for preconception risk assessment and assess their reliability, validity and acceptability.*

- *Develop research strategies for improved diagnostics, new therapeutics and vaccines, passive inmmunotherapy, and community prevention and control programs for influenza, pertussis, meningitis, rotavirus, cholera and other enteric bacteria and viruses that cause severe diarrheal illness.*

- *Investigate the causes and epidemiology of childhood developmental disorders, including diagnosis, prevention and treatment.*

Strategic Alliances

- *Develop a technical partnership with the United Nations Foundation Programme Framework on Children's Health, focused on improving public health systems in low- and middle-income nations, the USAID Child Survival program and other health service arms.*

Nutrition

A correlative research challenge is to better understand the role of nutrition on health, physical development and learning. It is estimated that 350-500 million people throughout the developing world are at nutritional risk due to marginal access to a basic diet and constant catabolic demands due to frequent infectious diseases. Deficiencies of micronutrients are attributed to a variety of conditions, such as blindness due to severe Vitamin A deficiency, anemia due to iron deficiency, and growth faltering due to zinc deficiency; and all three may condition the host for an increased burden of morbidity and mortality due to infectious diseases. There is increasing appreciation of the actual or potential systemic impact of nutritional deficiencies on a broad range of health problems. For example, malnutrition is estimated to be an underlying cause of at least half of childhood deaths under 15 years in low- and middle-income nations, resulting from perinatal causes, respiratory and diarrheal infection, measles, malaria and other infectious diseases.

Vitamin A alone is hypothesized to cause broad systemic effects in the body, among them reduced ability to resist influenza, compromised epithelial cell function in the gastrointestinal and respiratory tract, and the increased risk of bacterial colonization in vulnerable organ systems. Zinc plays a key role in the growth, development and functioning of netrophils, macrophages, natural killer cells, and T and B lymphocytes, suggesting the importance of zinc status in immune function. Selenium, an essential trace element, also appears to influence the function of T lymphocytes and may have a role in host immune response. Low circulating micronutrient levels have been described in all states of HIV infections: plasma or serum levels of intake of

vitamins A, E, selenium, and zinc have been associated with increased disease progression and mortality.

Because these and other findings hold enormous significance in shaping priorities for prevention programs, hypotheses regarding the systemic effects of micronutrient deficiency require testing and confirmation in various settings, to include sophisticated measures of specific micronutrients, dietary intake, and body composition. There is a need to perform longitudinal assessments of nutrition status at one or more sites in low- and middle-income nations along the model of the Framingham and Nurses studies. An alternative approach would be to extend selected epidemiological investigations to include measurements of nutritional status (e.g., examining the relationship between nutritional status and morbidity associated with malaria in preschool children).

Program Development Goals and Related Training Needs

- *Understand the relative importance of increased nutrient intake and control of infectious disease as a means to reduce malnutrition.*

- *Support intervention research to ameliorate/prevent chronic and acute diseases through nutritional intervention.*

- *Understand nutrient-gene-environmental interactions in in-utero.*

- *Better define age-related decrements in function, early markers of disease risk and biomarkers of dietary intake in selected populations.*

Strategic Alliances

- *Organize NIH international working group on nutrition to conceive a trans-NIH initiative based on common interests of NIH institutes which support nutritional sciences*.

- *Convene an intrasectoral planning group on prevention of low birth weight in low-income nations to include specialized UN agencies, the UN University Hunger Programme, USAID, the World Bank, USDA, selected foundations and industry. The intent would be to review state-of-the-art knowledge on interventions, algorithms and policies that reduce the risk of low birth weight and identify research needs and strategic alliances.*

III. INFECTIONS AND IMMUNITY: THE CONTINUALLY CHANGING THREAT OF MICROBIAL DISEASES

HIV/AIDS

The AIDS pandemic represents what some speculate is the beginning of a disturbing trend: the epidemiological transition of a localized disease affecting a community into a global health problem. The global resurgence of clinical tuberculosis is a disturbing sequel. Over 90 percent of the world's estimated 35 million people infected with HIV live in low- and middle-income nations, including the highest rates of AIDS infection for pregnant women and children. In many African nations the pandemic is a leading cause of adult death. Apart from the humanitarian toll, HIV has disrupted economies, and placed tremendous stresses on health care systems—in Asia it is a ticking time bomb.

Due to the genetic variability of HIV and geographic differences in its epidemiological features, the development of effective vaccines will require efficacy trials in low- and middle-income nations. It is probable that a future vaccine will incorporate viral antigens from several geographic regions, or that vaccines specific to individual regions will need to be developed. Eliciting an immune response of the optimal type, of sufficient magnitude and duration remains the enduring obstacle to an effective candidate vaccine. Vaccine development has been impeded by gaps in our understanding of the biology of HIV infection, the high mutation rate of RNA viruses creating new variants against which to engender protection, and the lack of non-primate animal models which predict the human response. Despite significant strides in understanding the molecular composition, structure and behavior of HIV, further knowledge is required on the precise nature of the retrovirus and how it invades cells and multiplies and develops resistance to therapeutic agents. As a result, more novel approaches to basic investigation may be pursued as a means of shedding new light on HIV pathogenesis, new therapeutic targets, and host response. In low- and middle-income nations, this might include studies on other infectious agents and on microbial pathogenesis in general, as well as expanded research on opportunistic infections.

An evolving global strategy for HIV/AIDS is to deploy multiple prevention strategies based on successfully tested interventions: in concept, to prevent HIV at the population level through "combination" approaches. The development of a comprehensive HIV prevention science agenda is one of the early recommendations of the NIH AIDS Research Program Evaluation Working Group of the Office of AIDS Research Advisory Council. Until an effective HIV vaccine is available, it is imperative to create lower cost "prevention algorithms" to contain HIV in highly impacted countries through the testing of combination interventions to include STD treatments, topical microbicides, condoms, improved obstetrical practices and behavioral/social interventions, all the while viral, immunologic, and other clinical science investigations are pursued.

AIDS INTERNATIONAL RESEARCH AND TRAINING PROGRAM

The AIDS International Training and Research Program (AITRP) represents the international training arm of NIH's HIV research effort and continues to increase the international research capacity of our domestic institutions, as well as those of developing nations. The scope of AITRP reflects the extent of the pandemic in developing nations. As noted, over the ten-year course of this program 1,300 scientists from over 80 nations have trained in the U.S. and many have participated in NIH research protocols, both in the U.S. and on their return home. One indicator of progress is the success of the program in generating scientific findings and resulting publications. Last fiscal year, FIC trainees authored or co-authored over one hundred papers in prominent scientific journals. To date, there have been several key areas of emphasis, as summarized below:

First, FIC trainees have monitored HIV variants and provided epidemiological data ultimately required for the production of candidate vaccines and the design and evaluation of vaccine efficacy trials. The program now has established a core of highly trained clinical and epidemiological investigators in regions of the world that may become the site of international HIV vaccine trials when such a vaccine is available for widespread testing. These scientists also are positioned to support other HIV interventions, such as anti-viral treatments, microbicides, and programs to modify high-risk behaviors. This has been accomplished through the close collaboration with the NIAID HIVNET program, which has established a baseline of epidemiological data and cohorts of volunteers for future vaccine trials.

Second, FIC trainees have conducted studies on HIV susceptibility among individuals with repeated risk exposures who remain uninfected. These studies have been undertaken in Kenya and Senegal in cooperation with the University of Washington and Harvard University. Longitudinal research in Kenya indicates that some commercial sex workers with repeated HIV exposures have remained seronegative; and it is speculated that these individuals may be innately resistant to HIV or have acquired some form of protective immunity. In Senegal, some high risk groups with HIV 2 infection (a less virulent form of the virus) had a lower incidence of subsequent HIV1 infection, suggesting a potential for a cross-protective mechanisms (similar in theory to the protective influence of cowpox on smallpox infection-the basis of the smallpox vaccine). These separate findings remain preliminary, but may enable scientists to better understand factors related to immune response to HIV.

Third, FIC has supported efforts to understand factors related to maternal-fetal transmission of the virus, including the role of maternal immunity in the prevention of transmission and the role of co-infection. In fact, approximately one half of the international studies underway to reduce HIV transmission from mother-to-child are associated with the AITRP program. In particular, through studies led by Johns Hopkins and Harvard Universities the AITRP has stimulated research on nutritional supplementation with micronutrients as an approach to decrease mother-to-child transmission of HIV.

And finally, AITRP has provided findings on prevention of opportunistic diseases resulting from HIV infection. The study cited in our testimony provides early evidence that a preventive regimen of the antitubercular agent Isoniazid (INH) reduces the risk of active tuberculosis in patients who are PPD and HIV positive. The prospective benefits are two-fold. The regimens may improve the clinical outlook for HIV patients, and could reduce the risk of TB infection in the community at large by reducing active TB cases among HIV positive individuals.

The current FIC program in this area is the *AIDS International Training and Research Program*, co-sponsored by the National Institute of Allergy and Infectious Disease and National Institute of Mental Health. The program enables US institutions to pursue a range of programs with low- and middle-income nations, including field and laboratory-based studies, training fellowships and regional workshops.

Program Development Goals and Related Training Needs

- *Assist to develop the research infrastructure, cohorts of study volunteers, and field and laboratory skills to support international HIV vaccine and therapeutic trials.*

- *Define the shortest course (e.g., intrapartum or newborn only) of antiretroviral therapy that is feasible and effective in reducing perinatal transmission.*

- *Evaluate simple and feasible interventions other than antiretoviral agents for their efficacy in diminishing maternal/infant transmission.*

- *Pursue culturally germane behavioral and social interventions to reduce risk of sexual and parenteral transmission.*

- *Identify strategies in resource-poor settings to reduce the risk of HIV infections through blood transfusion.*

- *Examine HIV susceptibility among individuals with repeated exposures who remain uninfected, in order to determine factors related to resistance, including mucosal immunity, viral, genetic, and other immunologic factors, and endocrinological factors.*

- *Examine factors related to maternal-fetal transmission, including whether specific strains of the virus are more likely to be transmitted, the role of maternal immunity in prevention of transmission, and the role of co-infections.*

- *Monitor changes in the virus, including genetic, serologic, and functional variation in support of the design of candidate vaccines.*

Strategic Alliances

- *Establish cooperative ties among FIC HIV research training centers and the NIH Vaccine Research Center, which is dedicated to the creation of novel vaccine vectors and immunogens and new vaccine strategies against HIV.*

- *Encourage greater involvement of basic and clinical research departments within US medical schools with HIV research sponsorship from NIH, including the Centers for AIDS Research (CFAR) program institutions.*

- *Develop linkages with other global clinical trials groups to coordinate collaborations for multicenter trials and aggregated data analyses.*

Emerging Infectious Disease

The AIDS pandemic has been-described as an object lesson in the difficulties of coping with a new or newly recognized virus. It is one of several infectious diseases that have emerged due to environmental and social change and microbial adaptation. Examples include chloroquine resistant malaria, a new cholera variant, Ebola virus, Marburg disease, Lassa and Rift Valley Fever and O'Nyong-nyong encephalitis. Further, there is the potential of new hepatitis virus variants that circumvent vaccine protection. Hepatitis B, similar to HIV and other viruses which use reverse transcriptase to replicate, undergoes rapid genetic change.

Global capabilities for disease surveillance and rapid response are seriously fragmented. Some speculate that if a state-of-the-art disease surveillance program existed in Central Africa in the 1970's, the silent spread of HIV may have been identified earlier and preventive measures devised. There is a need for a network of research groups in low- and middle-income nations to identify unusual clusters of disease, conduct laboratory and field investigations and test interventions. While it is impractical to conduct a pan-continental surveillance, these groups might be situated where the potential for emerging infectious disease is greatest, due to

population densities or encroachments on natural ecosystems, such as rain forest. This network would represent laboratory and diagnostic facilities to examine specimens, identify isolates, prepare and distribute reagents and develop physical and molecular markers for identification. The foundation for such a network may already exist through laboratories supported by the National Institutes of Health, Centers for Disease Control and Prevention, the Pasteur Institutes, Wellcome Trust, British Medical Research Council, WHO collaborating centers, and Rockefeller University International Clinical Epidemiology Network (INCLEN), among others.

Leadership in Global Health: Malaria

Each year, malaria kills over 1.5 million individuals, mostly children under the age of 5 living in Africa. Morbidity due to malaria is also significant and it leads to measurable losses of economic productivity in endemic countries. Attempts to control and prevent malaria have suffered due to an incomplete understanding of the interactions between the parasite and its human and mosquito hosts, the development of anti-malarial drug resistance, mosquito insecticide resistance, inadequate patient management and the decline in prevention efforts. The Multilateral Initiative on Malaria (MIM), an alliance of science funding agencies and African partners, was launched with major support from NIH to address critical needs in malaria research and training. FIC is serving as the Secretariat for the MIM and is working to advance its agenda with a range of domestic and international groups. FIC is also initiating a new research and training program to support U.S.-based university malaria researchers. The goal of this program is to train and expand the capabilities of scientists and health professionals from malaria endemic countries to engage in malaria research at their home institutions and in partnership with US collaborators.

The application of new epidemiological tools would be an essential objective. Powerful analytic techniques now available include molecular genetic probes (used to identify hepatitis C and hepatitis delta agents) polymerase chain reaction (used to identify Hanta virus) and new methods under development for other types of pathogens. Antibody and antigen detection strategies are evolving rapidly to include optical imaging as well as chemi-luminescence using compounds based on diozetane chemistries.

There is a recognized need to integrate health into environmental monitoring systems. It is likely that several vector-borne diseases may be influenced by climate change. These diseases include malaria, lymphatic filariasis, African trypanosomiasis and yellow fever. It is hypothesized that as global warming isotherms shift poleward, the range of vector-borne diseases may expand. Global climate change also may increase the risk of parasitic diseases at higher elevations. Disease surveillance laboratories including GIS surveillance systems might analyze climate and precipitation trends and their effect on vector populations, as well as other factors which influence terrestrial ecology.

The capacity to prevent or contain the spread of disease pathogens also depends on the identification of reservoirs of drug-resistant strains of microbes. The emergence of these strains is due largely to selection pressure on organisms continually challenged by antibiotics and chemo-therapeutic agents. Although microbes have expressed antibiotic resistance, even before the widespread introduction of antimicrobials, selection pressures have enhanced their emergence and spread.

Drug-resistant microbes impede capacity to treat tuberculosis, malaria, meningitis, shigella and schistosomiasis, among other infectious diseases. While research approaches to circumvent drug resistance in bacterial and viral infections are only now evolving, some drug companies are beginning to design "rational" drugs that employ selective mechanisms to destroy specific microbes. This is a departure from more conventional screening procedures to determine anti-bacterial and anti-viral properties. Clinical progress in this field will rely on more fundamental research on basic biological mechanisms that underlie antibiotic resistance. In support of these efforts, research-based surveillance efforts in low- and middle-income nations may provide initial insights into putative agents and pathogenesis.

Current FIC programs in these areas are *the International Training and Research Program on Emerging Infectious Diseases* and *Actions to Build Capacity Initiative* and the *Environmental Ecology and Emerging Infectious Diseases Research* programs. These programs enable US institutions to pursue a range of activities with low- and middle-income nations, including field and laboratory-based studies, training fellowships and regional workshops.

Program Development Goals and Related Training Needs

- *Through global collaborations establish "sentinel sites" to develop data and predictive models to anticipate future epidemics and devise corrective actions. Epidemiological research and surveillance will be pursued for new microbial outbreaks or the re-emergence of recognized microbes, where the potential for new epidemics is greatest. These laboratories will standardize methodologies and share essential reagents.*

- *Evaluate methods to diagnose infection, isolate or culture infectious agents, and monitor for genetic, serologic and functional variation in these agents at study sites.*

- *Develop techniques for rapid diagnosis and model systems to predict the spread of emerging diseases.*

- *Strengthen communication systems through use of new satellite technologies which provide two way communications with remote ground stations, or Internet linkages.*

Strategic Alliances

- *Establish an international working group of Federal agencies, academic institutions and industry to develop model universal practice guidelines for antimicrobial use and model curricula for training of health and veterinary professionals in antibiotic usage.*

- *In cooperation with Federal agencies and international organizations, integrate health into existing and planned environmental monitoring systems, deploying such approaches as monitoring of disease vectors, identification of biological markers of early warning, and remote sensing.*

- *Encourage greater involvement of basic and clinical research departments of medical schools with research sponsorship from NIH related to microbial change and adaptation.*

Factors contributing to disease re-emergence and examples of associated infections

Contributing factors	**Associated infectious diseases**
Human demographics and behaviour	Dengue/dengue haemorrhagic fever, malaria, sexually transmitted diseases including HIV, giardiasis
Technology and industry	Toxic shock syndrome, nosocomial (hospital-acquired) infections, haemorrhagic colitis/haemolytic uraemic syndrome, food borne infections
Economic development and land use	Lyme disease, malaria, plague, rabies, yellow fever, Rift Valley fever, schistosomiasis
International travel and commerce	Malaria, cholera, pneumococcal pneumonia, diarrheal diseases, influenza
Microbial adaptation and change	Influenza, HIV-1, malaria, *Shigella*, cholera, *S aureus*, enterobacteriaceae
Breakdown of public-health measures	Rabies, tuberculosis, trench fever, diphtheria, whooping cough (pertussis), diarrheal diseases

Source: adapted from Committee on International Science, Engineering, and Technology (CISET), 1995.

Tuberculosis

Perhaps one of the most intractable pathogens is the tubercle bacillus, which accounts for one-quarter of preventable deaths in the developing world. Although effective control programs can achieve significant cure rates, treatment requires multi-drug regimens of antibiotics taken over at least a six month period. Of especial urgency is the global emergence of drug-resistant *M. Tuberculosis*, largely the result of poor compliance to treatment. This has generated drug resistant strains that outlive interrupted treatment regimens. The resurgence of TB is due only in part to the HIV pandemic, which has activated latent TB infection in HIV carriers and expanded the disease reservoir. Increased prevalence is also the result of complacency among industrialized nations, due to premature confidence in antibiotics, and a continuing erosion of public health services in regions of the developed and developing world. Although the Bacille Camette-Guerin (BCG) vaccine has prevented tuberculosis meningitis and disseminated TB in children, it is of only limited effectiveness in preventing pulmonary tuberculosis in adults.

The current FIC programs in this area is the *Tuberculosis International Training and Research Program*. The program enables US institutions to pursue a range of tuberculosis-focused programs with low- and middle-income nations, including field and laboratory-based studies, training fellowships and regional workshops.

Program Development Goals and Related Training Needs

- *Develop strategies to extend the coverage of directly observed treatment, short-course (DOTS) for tuberculosis.*
- *Study new approaches to preventive therapy, including immunotherapeutic interventions.*

- *Identify alternative methods of drug delivery, such as incorporation of drugs into liposomes or controlled release formulations; development of new preventive vaccines and specific and rapid diagnostic agents.*

- *Conduct operational studies on the design and management of TB control programs in low- and middle-income nations*.

Vaccine Development and Delivery

Historically, vaccines have provided perhaps the most effective tool for disease control and prevention. In low- and middle-income nations vaccines have eradicated smallpox and constrained the spread of measles, poliomyelitis, yellow fever, diphtheria and tetanus. Nonetheless, at least three million children die each year of vaccine preventable infections because these available, tested, safe and effective measures are never delivered to them. Furthermore, a striking disparity exists between the small cluster of diseases that can be prevented by current vaccines, in comparison to the many infectious agents for which no vaccine is available. The gap could narrow rapidly with a new generation of immunization strategies developed through recombinant DNA techniques, the production of monoclonal antibodies by hybridomas, nucleic acid sequencing and peptide synthesis. Progress will depend on field trials in regions of the world with high attack rates for specific diseases, and the development of public-private partnerships to target vaccines for the poor and for tropical diseases.

The public has assumed significant responsibility for vaccine development, due to liability concerns facing private manufacturers. The Public Health Service takes a lead role in basic research leading to discovery of vaccine candidates that must be further developed by industry. Moreover, trials that require field sites in low- and middle-income nations are perhaps most appropriately pursued by the public sector, due to political considerations and ethical complexities, although private firms have taken on this role and responsibility in the past. Obligations to foreign populations and host nations participating in clinical trials, especially in regard to health care and access to successfully tested vaccines now requires a deep public involvement in such studies in the future. In pursuing immunization strategies, it is of long-term benefit for scientists from low- and middle-income nations to participate in the spectrum of vaccine research. This not only includes the design and conduct of efficacy trials, but more basic studies on the biology of the pathogen and host, the nature of the immune response and new approaches to vaccine production (e.g., attenuated live bacterial vaccines, vectored multi antigen delivery systems, synthetic peptides and DNA and RNA vaccines for the future).

- **New Vaccines for Parasitic Diseases**

In 1955 WHO launched a plan for the eradication of malaria through indoor spraying of insecticides and use of synthetic antimalarial drugs. The local success but general failure of this plan represents the difficulties of coping with a complex and adaptable parasite through sustainable vector control and treatment, and the potential of immunization as perhaps the most viable long-term intervention. The development of a deliverable vaccine for malaria likely will require recombinant DNA approaches, DNA vaccines or synthesis of peptides, since culture of the parasite for antigen production is not possible except in limited quantity. Control of schistosomiasis presents similar research challenges to malaria, due to the complex life cycle of the parasite and the difficulty in engineering vaccines to induce the desired protective immune response. However, unlike malaria, the human infection can be readily replicated in

experimental murine models. Candidate vaccines for these infections are targeted to disrupt the life cycle of the parasite at one or more sites and more than one mechanism (e.g. antibody and cytotoxic T lymphocytes). Consensus is building that the capacity to evoke a sustained and effective immune response may require a multivalent vaccine that incorporates immunogens to disable the parasite at different stages of the life cycle.

The persistence of onchocerciasis also exemplifies the importance of immunization strategies. It is a leading cause of blindness in the world with approximately 20 million people infected and 400,000 blinded by this agent. Yet these statistics may obscure the real impact of the disease in hyperendemic areas, where half the males and one-third of the females over the age of 15 will be blinded by *Onchocerca* infestation. The disease ultimately transplants communities in areas with fertile soil and abundant water to sites with poor agricultural productivity. In some areas, acceptable vector control has been achieved through weekly applications of insecticide; and a new chemotherapeutic agent, Ivermectin, has been administered through a public-private partnership donation program with great success. Although dramatic decreases in ocular disease have been realized, several problems threaten to reverse these achievements. Insecticide resistant vectors have increased. Moreover, many areas of endemic onchocerciasis have terrain and hydrological characteristics less suited to vector control and drug resistance could emerge and threaten to reverse the progress to date. The eventual production of vaccines against *Onchocerca* infection and other parasitic helminths will require better understanding of host immune response and surface antigens, through epidemiology and molecular analysis of infection.

- **New and Improved Vaccines for Diarrheal and other Childhood Diseases**

A major cause of severe diarrhea in children is rotavirus. Although oral rehydration therapies remain a key public health tool, significant progress has been achieved in the field of vaccine development. This has lead to multivalent vaccines that immunize against various rotavirus strains. Other studies suggest the potential to increase the immunogenicity of the polysaccharide capsule of several diarrheal-related bacteria (*Salmonella, E. coli, Shigella)* in a single vaccine. These developments signal an important trend in vaccine research: the development of a multivalent vaccine that can provide immunity to several different disease pathogens.

The need to realize new scales of efficiency is significant. Fully protecting children with existing vaccines such as measles and DPT requires multiple visits to health facilities and delivery systems that are expensive and difficult to maintain. For example, over one-quarter of immunization costs worldwide represent cold-chain expenses to preserve vaccines prior to use. Recognition of these conceptual and practical challenges led to the Children's Vaccine Initiative to promote the development of a new generation of vaccines that are safe, heat stable, and can be administered orally in limited doses. Realizing this goal requires a broader understanding of cellular and molecular immune mechanisms of the gastrointestinal tract, among other challenges. Research needs include studies on the structure, function and regulation of immune mechanisms, such as immunogenetics, T cell receptors and cytokines.

- **New Vaccines for Viral-based Cancers**

A range of infectious agents now have been associated with human cancers. These include human papillomaviruses (cervical cancer), hepatitis B virus (liver cancer), human herpes virus (HHV) ((Kaposi's sarcoma), human B lymphotropic virus (lympho-proliferative disorders), human

T cell leukemia viruses (adult T cell leukemia), and Epstein Barr virus (Burkitt's lymphoma). For many of these conditions, an effective future intervention may be vaccination. Population-based research in low- and middle-income nations holds the potential to identify epitopes of certain viruses that elicit humoral and cellular immune responses. In addition, the potential may exist to develop an inexpensive hepatitis B vaccine that can be administered in universal childhood immunization programs in populations at greatest risk of HBV-related cancers.

Program Development Goals and Related Training Needs

- *Strengthen epidemiological research and clinical trials capacity at sites in low and middle-income nations that might serve to evaluate candidate vaccines for parasitic, bacterial and viral disease.*

- *Examine correlates of protection and surrogate markers to evaluate vaccine candidates and monitor vaccination; improve the stability of vaccines to avoid the need for storage at refrigeration temperatures (cold chain).*

- *Develop the most effective bacterial or viral carriers for systemic and mucosal immunization and improve the safety and efficacy of different vaccine adjuvant formulations.*

- *Develop preparations that allow controlled release of immunogens to be used as single-dose vaccines.*

- *Pursue measures to enhance passive immunity acquired in-utero to protect against infections acquired before active immunity can be generated.*

- *Evaluate the efficacy and economics of candidate conjugate pneumococcal vaccines in low-income countries.*

- *Evaluate the barriers to delivery of existing Haemophilus infuenzae type b vaccines in low- and middle-income countries.*

- *Develop and evaluate ways to increase efficiency in the Expanded Programme on Immunization by simplifying delivery and maximizing use of opportunities for immunization.*

Strategic Alliances

- *Pursue technical alliances with the formative Global Alliance for Vaccines and Immunization, launched in concert with UNICEF, WHO and the Gates Foundation to help guide resource allocations.*

- *Establish partnerships with the World Bank, WHO and relevant donor organizations to model the impact of selected vaccines on future disease burden and their cost-effectiveness.*

Population Biology

In the biological sciences, evolutionary theorems are helping to define complex problems, and in some instances, replacing sequential, or cause-and-effect models. A powerful example is the discipline of population biology. During the past decade, population and evolutionary biologists have established and refined quantitative methods and theories on the dynamics of numerous infectious agents. This emergent field has become a key practical tool in the investigation of the interplay of variables that influence the course of infection in the individual, and determine transmission in the community. Notably, the coordinated efforts of population biologists, immunologists, and virologists led to landmark findings on the rates of mutation and replication of HIV, and changed approaches to HIV treatment. Elegant mathematical models describing the nonlinear interaction between populations of HIV and of CD4 T cells enable scientists to elucidate the rapid viral replication underlying HIV infection. Prior to this landmark analysis, the low viral load during the asymptomatic phase of the infection was interpreted as a slowly replicating or dormant infection. However, these novel, quantitative analyses demonstrated how low viral load reflects a dynamic equilibrium between very high rates of production and clearance, a finding that resulted in new treatment modalities to slow the progression of HIV through early and aggressive anti-retroviral therapy.

In addition to contributing to our understanding of viral pathogenesis, population biologists have created quantitative models to model the course of infection in a population, predict the minimum duration of treatment required to eliminate viral infection, and to explain the differences in the rates at which drug resistance appears in the treatment of different infections. Models of the population dynamics of drug-resistant organisms are beginning to provide explanations for these phenomena, as well as probabilistic models on the impact of changes in antimicrobial use on the extent of resistance in individuals and populations. These methods also inform the design and targeting of vaccination programs by calculating the critical fraction of a population that must be vaccinated to eliminate a particular pathogen, or anticipating problematic sequelae of community-based vaccination (for example, increases in congenital rubella syndrome as vaccination increases the average age of rubella infection).

Quantitative and computational approaches to vaccine development and deployment will become more critical as immunization strategies become more complex. In particular, many current vaccines are directed at organisms with little antigenic variation; however, the new generation of vaccines will be directed at pathogens with considerable antigenic diversity, such as HIV, *Plasmodium* and *Streptococcus*. These challenges raise a number of new biological and evolutionary questions that require theoretical modeling. For example, how will populations of antigenically diverse parasites evolve in response to mass vaccination targeting, a subset of the antigenic variants, and how will this evolution affect the vaccine's benefits in reducing total disease?

To meet these analytic challenges, FIC is well-positioned to support a core intramural program on the NIH campus in population biology, with emphasis on infectious disease burdens. If realized, the program would represent a unique disciplinary addition to NIH's robust intramural program in immunology, virology, microbiology, microbial genetics and other relevant fields and would be intended as a resource for both intramural and extramural scientists alike. One

approach may be to initiate this effort with a pilot program of theoretical studies to mature to embrace laboratory and clinical studies.

Program Development Priorities

- *Form a scientific planning group to identify the research orientation of this novel program, composed of scientists pursuing mathematical and computational approaches to study interactions between pathogen and host, the spread and persistence of genotypes within the pathogen population and the dynamics of transmission.*

- *Establish cooperative agreements with academic centers to support visiting appointments for domestic and foreign investigators in the field of population biology of infectious diseases*.

IV. BIOLOGY AND THE ENVIRONMENT

Understanding the Influences and Effects of Environment on Health

New infectious diseases emerge from a broad pattern of ecological relationships conditioned by environmental change creating both real and potential health threats. Equally insidious health risks are presented by rising concentrations of industrial and chemical pollutants. Environmental toxins are increasingly recognized as important factors in the etiology of cancer, respiratory disease, kidney disease, autoimmune and developmental disorders. Many adult chronic diseases may be linked with prenatal exposures to environmental toxins. For example, cervical cancers and reproductive dysfunctions occur in women exposed to diethylstilbestrol (DES) before birth. A related concern is the continuing environmental threat resulting from industrial accidents, including radiation exposure, and the health impact of global climate change due to ozone depletion and increasing levels of atmospheric $C0_2$.

These hazards are transnational in scope. They underscore the importance of international cooperation to identify and validate biological markers for environmentally-induced diseases and to develop interventions to prevent diseases in populations with known toxic exposures. The potential adverse health effects resulting from exposures to environmental chemicals are often first identified in populations of other countries. These include studies on the carcinogenicity of dioxin, the neurotoxic effects of methylmercury and the reproductive toxicity of polychlorinated biphenyls used in electrical wiring. Countries within the former Soviet sphere and regions undergoing rapid industrial transformation present unprecedented opportunities to understand, mitigate and prevent the health effects of environmental damage.

The FIC program in this area is the *International Training and Research Program on Environmental and Occupational Health*, co-sponsored by the National Institute for Environmental Health Sciences and the Centers for Disease Control and Prevention. This program enables US institutions to pursue a range of activities with low- and middle-income nations, including field and laboratory-based studies, training fellowships and regional workshops.

Program Development Goals and Related Training Needs

- *Foster international cooperation to identify the mechanisms of toxicity, radiation damage and DNA repair through multidisciplinary studies among populations with toxic exposures.*

- *Foster international cooperation to identify genes responsible for predispositions to toxicity and the effects of environmental agents on genes and gene products, cell function, communication, and regulation, embryogenesis and other integrated biological systems.*

- *Investigate the inflammatory response to environmental agents and the development of chromic pulmonary diseases.*

- *Study the role of nutritional status in susceptibility to environmental toxicants.*

- *Develop biomarkers of environmental exposure and effect.*

Strategic Alliances

- *Work with Federal agencies and international organizations to improve the emergency response mechanism to address newly identified international environmental threats.*

- *Encourage greater involvement of basic and clinical research departments of medical schools with research sponsorship from NIH to examine primary and secondary effects of environmental agents on human health.*

Biodiversity and Human Health

Biological diversity, which already is being reduced by human activity, may be the chief casualty of demographic pressure and environmental change. Some estimate that biological diversity is at its lowest level since the end of the Mesozoic age 65 million years ago. E.O. Wilson of Harvard University, one of our leading commentators on this crisis, has noted that the loss of biodiversity is the most important process of environmental change, because it is the only process that is wholly irreversible. The obstacles to reversing this trend are formidable and require creative solutions, since most endangered habitats are found in regions where population and economic pressures result in the contraction of natural ecosystems.

One prospective casualty is the loss of potential new medicines derived from biological resources such as plants, invertebrates and marine organisms. Although natural products have formed the basis of medicinal therapies for millennia, interest and pharmaceutical investment has resurged as a result of technological advances in both natural products chemistry and combinatorial chemistry, a new discipline enabling the synthesis of new derivatives with unprecedented speed and efficiency.

Scientists discovered the bioactive properties of a plant indigenous to Madagascar that produces two alkaloids (vinblastine and vincristine) that cure most victims of two of the deadliest cancers, Hodgkin's disease and acute lymphocytic leukemia. The anti-cancer agent Taxol was derived from the Pacific Yew tree. Another possible anti-cancer drug, halichondrin, has been found in a species of New Zealand sponge. And one of the most important classes of anti-hypertensive agents, angiotensin converting enzyme (ACE) inhibitors, are based on the venom of snakes from Malaysia and South America. Skin secretions from frogs are the source of hundreds of alkaloids useful in both drug development and neurobiology research. This research may be especially timely, since this particular family of frogs is threatened by destruction of tropical rainforests in Central and South America. Moreover, basic research in biodiversity has given us some of our most powerful research tools. Our entire biotechnology industry is founded on the use of restriction endonucleases, derived from bacterial biodiversity. The enzymes enable scientists to isolate a gene that has been identified in the hereditary material of an organism. Other species of thermophilic bacteria discovered in hot springs gave us heat-tolerant enzymes - the core discovery that made the polymerase chain reaction, or PCR, possible. In essence, PCR is a way to make many copies of short stretches of DNA without having to clone them. It has been invaluable to the study of genetics and the development of recent diagnostics, including highly sensitive tests for HIV infection.

In tandem with research to develop natural products, strategies are needed to preserve biological diversity and promote economic growth through sustainable use of wild and managed resources. The obstacles to reversing this trend are formidable and require creative solutions,

since most endanger habitats are found in regions where population and economic pressures result in the contraction of natural ecosystems.

The FIC program in this area is the *International Cooperative Biodiversity Groups*, supported in partnership with several NIH institutes and the National Science Foundation. The program represents international consortia of academic institutions, foundations and pharmaceutical companies that endeavor to discover new therapeutic agents from natural products.

Program Development Goals and Related Training Needs

- *Establish inventories of biological resources and contribute toward documentation and recognition of biodiversity.*

- *Develop novel approaches that emphasize equitable distribution of intellectual property resulting form collaborative efforts and commercialization agreements that benefit countries form which products originate.*

- *Identify strategies to enhance conservation management of biodiverse resources at study sites.*

- *Examine the potential of combinatorial chemistry to improve the capacity of low- and middle-income nations to synthesize new derivatives.*

Strategic Alliances

- *In concert with development agencies, promote efforts to quantify the health and social cost of environmental degradation as part of ongoing economic monitoring.*

- *In collaboration with academic institutions in developed and developing nations together with industry to bioprospect for new drugs under prearranged agreements for sharing of the economic gains of successful products brought to market.*

The Ecological Determinants of Infectious Diseases

Over the past twenty years unprecedented rates of change in diversity of non-human biota have coincided with the emergence and reemergence of numerous infectious diseases around the world. Virtually all of the world's terrestrial and aquatic communities and ecosystems have undergone dramatic changes in biodiversity, due primarily to habitat transformation (deforestation, reforestation, agricultural intensification, fragmentation), invasions of exotic species and chemical contamination. The coincidence of broad scale biodiversity changes and emergence of infectious diseases may be accidental, or it may point to underlying ecological relationships.

The role of biological diversity and habitat structure in stabilizing communities of plants, animals and micro-organisms has received a great deal of attention from ecologists in recent years. As a result, our capacity to analyze and model ecological dynamics and evaluate spatial and temporal aspects of environmental change has become increasingly sophisticated. Few, if any of these advances in ecological science have yet to contribute to biomedical or agricultural research and public health. In a parallel fashion, advances in our ability to define the molecular identity of parasites, their vectors, and understand the immune systems of hosts have

contributed significantly to our understanding of epidemiology and transmission patterns. However, the relationship of these factors to population dynamics of disease reservoirs or the biotic and structural complexity of ecological systems in which transmission occurs remain poorly understood.

To better understand the consequences of changes in terrestrial and marine ecosystems on human health, FIC, NIAID, NIEHS, NIGMS, and the National Science Foundation have developed an interdisciplinary biodiversity-infectious disease research program. This program will bring together ecologists, small mammal biologists, biomedical scientists and epidemiologists to elucidate the underlying biology of habitat and biodiversity changes that may lead to increased disease prevalence in humans and fill an important gap in our understanding of these interrelated dynamics.

Program Development Goals and Related Training Needs

- *Examine how environmental variation influences distribution and adaptation of organisms and consequences for human health.*

- *Pursue studies of individual life-history patterns and predator-prey, host parasite and evolutionary relations.*

- *Examine relationships between biodiversity loss and microbial emergence.*

- *Examine characteristics of species and environments contributing to invasiveness, and to its likely consequences.*

- *Investigate dynamical processes using model biological systems.*

Strategic Alliances

- *Pursue cooperative arrangements with the proposed FIC intramural program in Population Biology of Infectious Diseases, emphasizing the modeling of dynamic systems in microbial emergence.*

V. CHRONIC AND DEGENERATIVE DISEASES: A NEGLECTED EPIDEMIC

In 1990 non-communicable diseases accounted for just over 40 percent of the global burden of disease and disability. By the year 2020, their share is expected to increase perhaps to as much as 60 percent, with the increase attributable to economic and demographic trends in low- and middle-income nations. Diseases such as tobacco-related cancers and mental health disorders are expected to eclipse infectious diseases as major causes of lost years of health life. The pace of this change and numbers affected will be dramatic. For example, in China, non-communicable diseases are expected to account for three-quarters of the disease burden in the next twenty years. In India, the second most populous nation, the burden of non-communicable disease is expected to double. In principle, many of these burdens may be averted by adapting cost-effective interventions which have been applied in industrialized nations. These include, for example, primary prevention programs to modify environmental and behavioral risk fact as well as programs for secondary prevention. However, the appropriate transfer of these interventions to low- and middle-income nations require expanded efforts to determine risk exposures and culturally-relevant interventions.

Smoking Prevention and Cessation

Hundreds of studies document the health risks of tobacco use, from exacerbation of asthma and perinatal complications to cardiovascular disease and stroke, lung and other cancers (larynx, oral cavity, pharynx, esophagus, pancreas, bladder, cervix, leukemia), and chronic obstructive pulmonary disease (chronic bronchitis and emphysema). Such findings -- and the resulting public education campaigns, cessation programs, legislation/regulation, taxation policies, lawsuits and counter-advertising campaigns -- have contributed to declining rates of tobacco consumption in many sectors of the industrialized world. However, tobacco use continues to rise in low- and middle-income countries. These regions offer unparalleled opportunities for the cigarette industry: huge populations, low awareness of health dangers, few restrictions on marketing, governments in need of foreign investment, and typically untapped markets of potential female smokers. The less-developed areas are also relatively free of tobacco control regulations, laws or litigation that threaten the industry in the US and other industrialized countries.

Worldwide, four million deaths each year are attributable to tobacco products. In low- and middle-income countries, more than half of all men and close to 10 percent of women smoke cigarettes; these figures are increasing. It is predicted that by 2020, seven of every 10 people killed by smoking will be in low- and middle-income countries. If current smoking patterns continue over the next three decades, the toll is expected to reach 10 million deaths per year, exceeding the current mortality from diarrheal diseases, malaria, pneumonia and tuberculosis combined.

In July 1998, WHO established the Tobacco Free Initiative in order to coordinate a global strategic response to tobacco control. One of its major goals is to commission policy research to support rapid, sustained and innovative actions. To this end, FIC, in cooperation with multiple partners at NIH will establish a research and training program to improve international efforts to control the tobacco epidemic.

Program Development Goals and Related Training Needs

- *Assess the burden of morbidity and mortality related to tobacco in low- and middle- income countries as a baseline against which to monitor control efforts and stimulate policy responses.*

- *Pursue research on the causes of smoking, the addictive nature of tobacco use, and behavioral factors associated with smoking uptake in low- and middle-income countries.*

- *Pursue research into the adaptation of demand reducing measures such as tax schemes, and bans on advertising and promotion.*

- *Gather data on price elasticity in low- and middle-income countries and estimates of the social and healthcare costs of tobacco use.*

Strategic Alliances

- *Establish a formal partnership between NIH and the WHO's Tobacco Free Initiative, identifying NIH's role in promoting research and analysis in support of a Framework Convention for Tobacco Control.*

Mental Health Disorders

Mental health disorders are an unseen epidemic in most low- and middle-income countries. Severe psychiatric disease affects at least two percent of the population and the lifetime probability of major mental illness is about ten percent. By the third decade of the coming century unipolar depression is projected to be the leading disease burden in low- and middle-income nations and the second most important cause worldwide. Even with limited diagnostic capacity, an estimated twenty percent of patients attending primary care facilities in low- and middle-income nations meet accepted criteria for depression of panic disorder (all age groups). Cultural and societal determinants of mental health are poorly understood and compounded by high levels of social disruption, including violence, dislocation, sexual abuse, natural disasters, rapid urbanization and other stressors. Psychotherapeutic strategies are complicated or precluded by problems of cost, administration and compliance.

In particular, psychiatric disorders are not easily recognized in children; yet in many cases, the mental disorders of childhood are the precursors of adult, or lifetime, mental illnesses. It is clear that understanding the causes and how best to intervene in these illnesses during childhood offers hope for preventing many cases of adult mental illness. Even when childhood disorders do not persist, they may distort a child's normal psychological and social development. In the US alone, as many as 10 million children are affected, and only 20 percent are treated; extrapolated globally, mental health disorders in children constitute a public health urgency of unappreciated magnitude.

Program Development Goals and Related Training Needs

- *Address the shortfall of well-trained clinical investigators and epidemiologists in mental health fields in low- and middle-income nations, as well as inadequate training for physicians and other mental health professionals.*

- *Pursue epidemiological data on the incidence of mental health disorders and risk factors, including socio-cultural determinants of mental health in societies undergoing transition to industrialized economies.*

- *Adapt, or develop, test and validate diagnostic tools that are culturally relevant.*

- *Examine culturally-targeted prevention algorithms and non-pharmacological interventions.*

- *Examine genetic influences on mental health disorders and gene-environmental interactions.*

- *Pursue cross-cultural studies on protective factors for childhood mental health, such as family and community support systems.*

VI. GLOBAL HEALTH IN THE INFORMATION AGE

Providing access to reliable health and scientific information is a cost effective and achievable strategy for sustainable improvement in health care and scientific capacity. Most low- and middle-income nations are entering a period of technological change, which will result in a transition from a more traditional library system to reliance on electronic access to international data networks through individual workstations. Technologies such as CD-ROM, Integrated Services Digital Network (ISDN), fiber optics, and satellite telecommunication networks such as the Internet ultimately will evolve as the technical backbone to the scientific and health care community in these countries. The rapid development of commercial satellite data networks hold potential to reach geographically remote sites; although this technology stream often bypasses low-income nations in configuring the size of geographic coverage.

- **Access to Health and Research Data and Analytic Tools**

Information technologies such as Internet provide a global platform for novel applications in biomedical research. The biomedical sciences, fundamentally, have been characterized as an information science in light of advances in human genetics: our understanding of genes as information storage units written in linear code, translatable into a sequence of amino acids and a resulting protein. Internet and analogous services will dramatically change the nature of transnational research, as research questions increasingly rely on high-performance computing and communications. The challenge for the global health research community will be to exploit the full range of informational tools to create "collaboratories," a term invented by William Wulf, President of the National Academy of Engineering, to describe groupings of researchers in a common field who share information, instruments, software and even computing capability through the information highway. This is a particularly efficient means of drawing scientists from low- and middle-income nations into the mainstream of Western science. An advanced prototype among industrialized nations is the interactive network among biologists who study the nematode worm, who share genomic data, bibliographic information and experimental notes in an organized format. This loose model can be adapted to a range of basic and population-based research pursuits. Continuing education opportunities in informatics, directed toward biomedical scientists in low- and middle-income countries may be a key means of fostering their participation in global science initiatives, including molecular and cell biology.

- **Decision Analysis and Rapid Response**

Databases developed by NIH and other technical agencies in the fields of toxicology, environmental health and infectious disease control are potential resources in emergencies and could be provided in real-time through emerging technologies. A compelling example is the lethal outbreak of cholera along the Rwandan frontier. The epidemic may have been mitigated if relief workers had gained access to treatment and control procedures through satellite-assisted support system. On the ground there is a need to establish computer-assisted information systems of treatment guidelines for integrated clinical services. Similar systems are required for immunization programs, family planning and obstetric services—each of which would benefit from factual data base and expert systems.

Physicians and health care professionals increasingly use computer communications technology to consult on medical issues, such as the diagnosis of complex or rare conditions. A digitized image (e.g., a CT scan) may be transmitted internationally for analysis. While these technologies have found limited application in low- and middle-income nations, their promise for geographically remote or medically underserved communities is considerable. Physicians in

remote regions may be able to take advice in real time from expert colleagues through video monitors. These technologies also offer the prospect of distance learning and training for health-care providers and health managers. Already, several expert networks have been created among institutions in low- and middle-income nations to provide guidance in such areas as malaria diagnosis (Cameroon), obstetrical complications (Malaysia) and perinatal care (Brazil). Moreover, there are several linkages between hospitals in the middle-income nations and US counterparts for teleradiology and telepathology services. Among other benefits, these networks serve to eliminate or reduce the cost of transferring patients for medical care abroad.

The current FIC program in this area is the *International Training in Medical Informatics Program*, co-sponsored by NIAID. The program assists scientists in low- and middle-income countries their U.S. collaborators to address local and global health needs through improved access to scientific and clinical information and improved research and surveillance capabilities. The objective is to train individuals who will apply state-of-the-art information and communication technologies to research and health surveillance activities and function in their home institutions as trainers or leaders.

Program Development Goals and Related Training Needs

- *Initiate "collaboratory" projects to link experts internationally on a given scientific challenge or process, such as infectious disease research surveillance, distance learning or peer review.*

- *Improve international access to national information resources through available technologies. Expand programs to ensure access to on-line databases (e.g., MEDLINE, TOXLINE) and related information processing tools by scientists and health care professionals.*

- *Develop training programs and workshops for end-users and search intermediaries.*

- *Initiate demonstration programs to connect U.S. academic medical centers with foreign institutions through Internet services. Services might include both database and electronic networking technologies.*

Strategic Alliances

- *Prompt discussions or negotiations to examine altruistic uses of commercial satellite data networks, so that scientific professionals and health care providers in low- and middle-income nations may be more fully incorporated in this technology stream*.

VII. PRIORITY TRAINING NEEDS IN LOW- AND MIDDLE-INCOME NATIONS: BUILDING THE FOUNDATION FOR EVIDENCE-BASED MEDICINE

Molecular Genetics and Genomics

Because of gains in the cost and efficiency of sequencing base pairs, the Human Genome Project is scheduled to complete a contiguous sequence in FY 2002. The genetic maps, physical maps and technologies that have emerged from the project already have had dramatic

effect on the research community's ability to discover genes underlying Mendelian disorders through positional cloning: identifying diseases by virtue of location in the genome rather than biochemical function. Prior to the project, only a small handful of disease loci had been identified. However, more that 100 loci have now been identified due to this strategy. One of the next generation initiatives of this project will be to characterize that less than 1 percent of our genetic make-up that represent variation through association studies. This project will include identifying points of variation between individuals known as Single Nucleotide Polymorphisms or SNPS. Comparisons of SNPS among different populations which have been isolated for long periods of time could potentially be useful in locating genes for common diseases. In tandem, there is a need to examine the ethical and social implications of human sequence variation on international populations, ranging from issues of consent and confidentiality to broader philosophic considerations.

The potential also exists to understand how gene expression influences susceptibility or resistance to infectious and chronic diseases. Population-based molecular epidemiology will be able to take advantage of the many novel molecular genetic techniques developed as result of sequencing the human genome. These molecular tools include DNA fingerprinting and variable number tandem repeat (VNTR) analysis. When used in conjunction with surveillance data, molecular epidemiological information could also be invaluable in tracking emerging infectious diseases and identifying multi-drug resistant microbes. Other efforts involving molecular research are focused on links between the genetic susceptibility, the environment, infections, chronic diseases and cancer. For example, the results of recent work on inheritance of susceptibility to malaria suggest that—in what is considered a relatively short period of evolutionary history—a remarkably diverse series of gene families have been modified in response to the selective drive of this infectious disease, involving the immune system, cytokines and other systems. These types of analyses are extending to mycobacterial disease—tuberculosis and leprosy—chronic liver disease and hepatocellular carcinoma associated with hepatitis B infection.

Since the vast majority of genetics specialists worldwide work in developed countries, efforts will be needed to train scientists in molecular biology and molecular epidemiology in host countries where research collaborations are conducted. Long-term efforts will be required, in order to provide continued adaptation of novel techniques in order to build sustainable capacity

Program Development Goals and Related Training Needs

- *Transfer research skills required to identify the specific location and behavior of genes; and define the multiple biological steps and interactions—cellular and environmental-- responsible for polygenic conditions, such as cancer and hypertension.*

- *Pursue studies to identify genes responsible for relative susceptibility and resistance to heritable, chronic and infectious disease burdens in low- and middle-income nations and test the predictive strength of particular polymorphisms with prospective community-based studies.*

- *Develop a cadre of scientists in low and middle-income countries capable of assisting in the design and analysis of linkage, linkage disequilibrium, and association studies on DNA sequence variation in specific ethnic groups.*

- *Pursue empirical studies on social and ethical considerations in genomic research analysis and interpretation, such as issues of consent and confidentiality, social stigma, and concepts of race, ethnicity and culture.*

Clinical Research and Management

Scientific methods that have enabled investigators to explore macromolecules--DNA, RNA and protein-are being applied to virtually all fields of clinical investigation. In complement with more classical techniques, these developments will influence profoundly the scope of clinical investigation in international health. These trials will require a well-trained cadre of scientists in low- and middle-income economies to cooperate with U.S. counterparts in the planning, design and conduct of clinical investigation, including epidemiological and behavioral studies. FIC will expand its scope of institutional training grants to support supervised study and research for clinically trained professionals from low- and middle-income countries. Curriculum topics will include clinical trials design, observational study design, bioethics, biostatistics, specialized courses in epidemiology, outcomes research, pharmacokinetics, computer-based training for data management and analysis and grantsmanship. Training international scientists alongside U.S. clinical researchers will facilitate collaborative clinical trials for the benefit of both populations.

Program Development Goals and Related Training Needs

- *Increase the pool of clinical researchers who can conduct patient oriented studies in low- and middle-income nations and become future mentors of clinical investigators.*

- *Emphasize curricula that prepare investigators to build the scientific bases for prevention of disease and management of established illness and improve methods of research, with attention to clinical variables essential to understanding the course of disease and the outcome of patient therapies.*

Strategic Alliances

- *Enter into a cooperative agreement with NIH Clinical Center to sponsor a pilot Mentored Research Career Development Award for physician-scientists from low-and middle-income countries.*

International Training in Bioethical Theory and Practice

Educating clinical investigators and health professionals in the culture of research ethics is integral to ensuring protection of human subjects in research. In coordination with other interested agencies, FIC will develop a training and career development initiative to increase the professional cadre of investigators and other health professionals with contemporary experience and understanding of ethical considerations, concepts and methods in human subjects research. Emphasis will be placed on programs in low- and middle-income nations where the need for such a professional cadre is greatest. The program will prepare candidates to assume professional roles or responsibilities as bioethicists in academic, clinical or public health settings and expand the skills and knowledge of clinical investigators responsible for ethics review or clinical trial design. Depending upon professional needs, curricula will include didactic training and participation in case conferences, ethics consultations and institutional review board deliberations.

The initiative will assist current and future investigators to pursue culturally relevant studies on ethical theory and practice in biomedical and behavioral research, and enable these individuals to provide expertise to their host institutions, national governments and international bodies. Efforts will be made to develop programmatic partnerships with research organizations in both western and non-western nations. Such a scheme will allow trainees to pursue curricula and conduct studies at multiple sites and expose candidates to diverse methodologies of moral reasoning, as well as multiple national systems guiding ethical conduct of human subjects research. The partnership also may assist trainees to perform comparative international studies (e.g., concepts of autonomy in informed consent procedures for vulnerable populations).

A second component of this initiative would be the sponsorship of regional bioethics workshops at sites in low- and middle-income countries. Cooperative proposals would be invited from investigators at two or more sites with investigators supported by NIH and partnering agencies. A principal objective of these courses will be to share expertise with biomedical and public health researchers responsible for ethics review. Workshops will address substantive and procedural decision-making of ethics review boards, such as risk-benefit analysis, levels of care for control groups, equitable selection of subjects, informed consent, and emerging issues in genetic epidemiology or the use of biological material, such as stored tissue. The benefits would be reciprocal: local ethics committee representatives will gain deeper insights into western models of ethics review, and the western participants will improve their understanding of local considerations in the interpretation and implementation of ethical precepts (for example, for NIH an objective may be to discuss adaptation of regulatory requirements for human subjects protection in NIH-sponsored international protocols).

Program Development Goals and Related Training Needs

- *Increase skills and knowledge in bioethics at the level of the community (prospective study populations), research investigator and allied health professional, ethics committee reviewers and institutional stewards (e.g., ministries of health).*

- *Increase the cadre of professionals in low- and middle-income nations capable of pursuing ethnographic studies of the practice of ethics in medical contexts—to deepen the empirical foundations of ethical practice and theory in transcultural research.*

Strategic Alliances

- *Establish an international consortium of institutions to serve as the loci for bioethics training. The consortium should represent institutions in all geographic regions and be governed by the participants.*

VIII. INTELLECTUAL CAPITAL: PREPARING THE NEXT GENERATION OF US SCIENTISTS TO MEET GLOBAL HEALTH CHALLENGES

Engaging our Underrepresented Minorities

To be effective, strategies aimed at increasing conferral rates at the baccalaureate and doctoral levels should place emphasis on populations for which significant increases can be anticipated. Underrepresented minorities, particularly African-Americans and Hispanics, make up one-quarter of the college-aged population and are estimated to constitute up 33 percent of the college-aged population by 2010. Yet in 1997, 5.2 percent of graduate students pursuing degrees in biological fields were African American, 3.6 percent were Hispanic. In 1995, 2.8 percent of scientists employed in biological fields were African American; that same percentage obtains for Hispanic-Americans.

FIC's role in nurturing our future generation of scientists encompasses innovative programs to support minority students from college through postdoctoral training. The *Minority International Research and Training* (MIRT) program provides opportunities for eligible undergraduates and doctoral candidates to pursue research at foreign institutions and study sites. Over the first five years of this program, an initial objective has been to reach a diverse group of U.S. academic institutions, ranging from Historically Black Colleges and Universities to research-intensive universities, and to create long-term partnerships with foreign institutions of excellence. A collateral aim has been to build consortia among participating U.S. institutions, especially among minority colleges and universities. This has served to orient promising students at minority colleges to the graduate school environment of major research universities. Such exposure may reduce psychological barriers that inhibit some students at minority colleges from progressing to doctoral programs in the biomedical sciences.

The MIRT program represents the first NIH effort to extend undergraduate training to foreign sites. Research techniques obtained by undergraduates through MIRT training include cell harvesting and culturing, protein assays, reverse chromosome painting, and X-ray diffraction and optimization. In addition, the program has introduced students to clinical challenges in international health.

Program Development Goals and Related Training Needs

- *Increase the cadre of talented students at both majority and minority colleges and universities who participate in scientific projects in low- and middle-income nations.*

- *Forge partnerships in international studies between colleges with predominately minority enrollments and research- intensive universities.*

- *Develop linkages between MIRT study groups and NIH international research protocols to give students exposure to the intellectual milieu of the research enterprise.*

- *Convene workshops on the NIH campus to enable MIRT students to present research results.*

- *Expand MIRT curriculum to include coursework in professional standards, rights of human subjects and welfare of animals.*

Strategic Alliances

- *Seek partnerships with Federal agencies, especially the National Science Foundation, and private Foundations such as the Howard Hughes Medical Institute, to expand the scientific scope of MIRT.*

Developing the New Cadre of International Health Specialists

Much has been written on the current and projected shortage of biomedical researchers in the United States who are engaged in tropical medicine. For example, previous reports by the Institute of Medicine have cited critical shortages in such fields as medical entomology, arboviruses and general parasitology. In part, these restrictions are due to reductions in the numbers of US sponsored laboratories at foreign sites supported by the Department of Defense, the US Public Health Service, the Rockefeller Foundation and other sponsors. Given the magnitude of global health challenges, there is a need to provide opportunities for young US investigators to perform basic and applied research within endemic countries, as well as provide a substantive career structure in global health research within US institutions. Several scientific developments provide enormous incentive to pursue research on disease burdens, which confront populations in tropical and sub-tropical regions. The first is the rapid sequencing of the genomes of pathogenic organisms, which will yield new immunogens and drug targets. A second is the development of new assays which enable scientists to measure biological changes at the genetic and molecular levels, and have created a powerful armature for population based studies.

To meet this need, *FIC's International Research Scientist Development Award* (IRSDA) is offered to U.S. postdoctoral biomedical scientists, in the formative stages of their careers, who seek an opportunity to continue research in, or extend their research experience into, developing countries. It provides the successful candidate with a period of mentored research as part of a strong, established collaboration between a U.S. sponsor and leading developing country scientists at an internationally recognized research institution. It is expected that, following this experience, the candidate will be able to pursue an independent and productive international research career, involving ongoing collaboration with developing country scientists, to more effectively pursue research relevant to stemming a major global health problem.

Program Development and Related Training Needs

- *Enhance the research skills of US postdoctoral scientists in laboratory-based, clinical and field investigation, including behavioral and ethnographic studies, through opportunities at foreign field sites.*

- *Create institutional linkages between research groups in the US and counterparts in tropical and sub-tropical sites training in the context of joint research projects.*

- *Promote stable career structures in global health research through US based "re-entry" awards to postdoctoral scientists pursuing research at foreign sites.*

Strategic Alliances

- *Along with other PHS agencies, explore the feasibility of an "international health corps" of scientists analogous to the now defunct PHS physician corps, which committed to serving underprivileged communities.*

IX. RESEARCH TO INFORM GLOBAL HEALTH POLICY

In addition to establishing priorities and goals for programmatic and special interest areas, FIC has identified a series of international policy priorities that bridge multiple sectors and influence the course and conduct of biomedical research. The Center will provide continuing analysis on cross-cutting policy issues and convene international fora on emerging scientific and medical challenges which require global strategies. Prominent among these are the following.

Health and Economic Development: The "Ratchet Effect" of Illness and Poverty

Over one hundred years after the industrial revolution, a large portion of the world remains impoverished. In the most compelling instance, the Organization for Economic Cooperation and Development indicates that the per capita income in Africa in 1992 was equivalent to that of Western Europe in 1820, and these disparities are widening. Correlates to economic development have been studied vigorously, but only modest attention has been paid to the relationship between health or demographic status and economic development. However, the foundations are strengthening in support of the widely-observed correlation between health and prosperity. Studies to link health and economic behavior have incorporated two broad avenues of investigation: macroeconomic studies to examine the relationship between country-level growth indicators and health, and microeconomic studies that explore the dynamics of health and productivity at the individual or household levels. Historical case studies have provided evidence that dietary improvements not only extend life spans, but significantly improve labor production rates, especially in the lowest quintile of the population.

These findings have been reinforced by household surveys that positively correlate nutritional status with income and labor supply. There is a corresponding need to understand how economic arrangements influence the quality of the social environment and human development. Through empirical studies of distributions of welfare in society, economists have demonstrated how wealth creation and allocation may determine the health and well-being of a population. For example, empirical research on famine and food supply and other studies have deepened understanding of social arrangements and economic deprivation and have demonstrated the limitations of more traditional indicators of economic performance. Similarly, studies among industrialized countries have correlated positively life expectancy with the degree of income equity within a society. The exploration of absolute and relative levels of income in society has significant implications for understanding of the relationship between wealth distribution and economic growth.

These studies represent only a subset of promising lines of investigation which converge in one summary conclusion: our conceptual understanding of the long-term influences on economic development and the formulation of effective policies relies on a deepened understanding of the determinants and consequences of public health. If governments and donors are to target effectively their investment in health as a component of development plans, expanded research is required on the complex dynamics of health, poverty and productivity. In this regard, biomedical and behavioral scientists are positioned to provide key empirical tools in concert with economic scientists and improve the quality of social and biological epidemiological data that support studies to measure and model economic outcomes. Promotion of health, reduction of disease burdens, alleviation of poverty, and enhanced productivity and education are the means to a safer, more stable and higher quality of life for all.

Program and Policy Development Goals and Related Training Needs

- *Assess the effect of biomedical interventions on household and aggregate economic indicators, including agricultural and manufacturing productivity, literacy and social and environmental welfare.*

- *Examine the influence of socio-economic factors on the effectiveness of medical and public health interventions.*

- *Assist in the development of a system of metrics that equips researchers and service providers with the information needed to effectively target public health interventions.*

- *Improve the quality and availability of health and economic data including longitudinal and inter-generational data-sets.*

- *Examine the effects of social capital and infant/childhood antecedents of adolescent and adult well-being in low- and middle-income nations.*

Strategic Alliances

- *Under the auspices of the WHO Commission on Macroeconomics and Health, form an annual health and economics network meeting to discuss methodological issues in extending the domain of economic theory and practice to biomedical disciplines--with the focused intent of improving and standardizing a system of metrics to measure individual health.*

- *In coordination with the World Bank's Global Development Network, form an alliance to examine the effects of health on economic growth, as well as the health outcomes of disparate economic and health policies in low- and middle-income nations, and participate in the training of development economists from the third world so that they will understand the relationship of health promotion to productivity and economic growth and work within their governments and in the International agencies to achieve that goal.*

- *Support linkages between NIH epidemiological investigation and studies to measure and model household economic outcomes.*

Bioethical Considerations in Transcultural Research

The international scientific community is confronted with complex questions concerning the content and conduct of cross-cultural research and the application of resulting health interventions in communities which have borne the research risks. In particular, the ethical design of clinical research jointly conducted between western sponsors and non-western host nations has generated a range of questions related to current ethical theory and practice. These span such substantive topics as clinical care for control groups, requirements for informed consent and considerations related to incentives and material inducements for research participation.

In all aspects of cross-cultural research, the scientific community is challenged to apply universal ethical standards of autonomy, beneficence and distributive justice to divergent

cultural settings, or more broadly, to reach an equilibrium between universal principles and acknowledgement of ethical pluralism within demarcated limits. As noted, FIC will extend its training efforts to the field of bioethics to assist scientists and institutions to design and review transcultural protocols. As a flanking initiative the FIC, WHO and interested partners have formed a *Global Forum on Bioethics in Research* as a common platform to support a continuing dialogue among international and national councils, which develop and promulgate ethical guidelines and the international research community. The objective of the *Forum* is to anticipate and address developments in the ethical design and conduct of cross-cultural studies. A key purpose will be to examine current and emerging considerations in interpreting and applying international codes and guidelines. The *Forum* is not intended to serve as a guideline-setting body--a function well-served by existing groups--but will provide a platform for shared analysis among international and national councils responsible for ethical guidance in biomedical research, as well as scientists from low- and middle-income and industrialized nations responsible for ethical review or protocol design, other experts, and community representatives.

Among practical outcomes, the *Forum* might result in operational mechanisms to resolve conflicts or uncertainties in ethical interpretation and implementation of international codes—a mechanism that several commentators have argued constitutes the logical next step in the international debate regarding cross-cultural research. The *Forum* also might offer a continuing means to examine scientific developments with implications for the future ethical design of human subjects research, such as emerging clinical trial methodologies or new vaccine modalities. One objective is to generate conceptual tools or models to inform ethical procedures. For example, creative methods are needed to translate concepts necessary for truly informed consent, such as randomization, placebo, disease causation and passage of time. Another important tool is an adaptable model of a "benefits-sharing" agreement to outline host and sponsor obligations and expectations at the inception of a clinical trial or observational study. The exercise itself may clarify the content of such *prima facie* obligations as "reasonable availability*" (Council of International Organization for Medical Sciences* guidelines) at the inception of the trial, or obligations incurred by sponsors for the training of local personnel or the support of local ethics review boards etc.

Policy Development Goals

- *Deepen the understanding of the influence of specific cultural, clinical, and economic settings on the ethical design of research.*

- *Adapt ethical procedures to local environments, such as risk/benefit assessment, informed consent and privacy and confidentiality.*

- *Define and design community involvement at different levels of study design, conduct and recruitment.*

- *Develop frameworks to assist researchers to apply principles of distributive justice, including clinical obligations to study participants and allocation of intellectual property rights or other benefits.*

Strategic Alliances

- *Expand institutional participation in the Global Forum of Bioethics in Research to ensure balanced geographic representation.*

- *Draw on the Global Forum for conceptual and operational guidance in the planning and implementation of the FIC training program in bioethics (described in Section VII)*

Intellectual Property Rights Protection

International treaties (e.g., Paris Union Convention, Patent Cooperation Treaty, Budapest Treaty) provide substantive and procedural protection for intellectual property. However, several factors limit the capacity of the US to protect intellectual property or market inventions abroad. A salient concern regards uncertainties in what constitutes patentable subject matter (e.g., criteria for determining the patentability of a composition of matter such as DNA or protein sequences), and ambiguities in disclosure provisions related to the deposit of scientific data to databases. Further, there are national differences in the interpretation of the patentability of life forms (other than microorganisms), notably between the US Patent and Trademark Office and the European Patent Office. A second concern regards procedural distinctions between the laws of various nations (e.g., first to invent vs. first to file, grace periods). And a third centers on the risks of patent infringement litigation given the web of partially overlapping patent claims.

Moreover, the US is concerned with the adequacy of current laws to protect against patent piracy, especially with regards to process patents. Although there have been initiatives to increase international disciplines to cope with these problems (e.g., WTO/TRIPs agreement), some governments (e.g., India, Brazil) view the international patent regimes as detrimental to domestic industries. In response, they resist granting protection for several sectors or limit the duration of patent protection on the grounds of national interest.

Policy Development Goals

- *In coordination with NIH's Office of Technology Transfer, provide continuing analysis of international developments which regards to intellectual property which influence transnational cooperation, including international trade agreements evolving definitions of patentable subject matter, material transfer agreements, licensing provisions and royalty rights, and negotiations on fair drug pricing.*

- *Create a greater coalition of government, academic, and private organizations to ensure that rights to intellectual property are modulated by the responsibility to insure the dissemination and use of drugs, vaccines, and technology developed with public support to the populations of the world in need of these discoveries now.*

Incentives for Technology Transfer to Low- and Middle-income Nations

- **Industrial Engagement**

Due to the expense of bringing a pharmaceutical to market, R&D expenditures are recaptured through pricing that considerably exceeds the marginal costs of production and packaging. As a result, inadequate incentive exists to invest in products where the prime market is the developing world and the potential of recovering costs is uncertain. This is perceived to impede the development of products that primarily benefit populations in low-income nations, such as malarial vaccines, microbicides or affordable STD diagnostics. Among therapeutic interventions licensed from 1975-1997, it is telling that only one percent are specific for tropical diseases. Economic constraints also affect the availability of essential drugs in many low-income nations.

It is estimated that approximately 2 billion people lack access to essential drugs. This is exacerbated by inappropriate use of drugs locally: for example, in Africa mothers of children infected with malaria may spend up to 30 percent of disposable income on treatments, fewer than half of which provide benefit. In addition, there is a need to create a more enabling economic environment for the deployment of available vaccines such as *Haemophilus influenzae* type b and hepatitis b, which will require novel funding or cost recovery schemes.

There is a well-recognized need to address these market challenges, which require consultation among multiple R&D sectors. At present, no forum exists to convene Federal agencies, pharmaceutical and biotechnology firms, relevant foundations and universities to examine impediments and incentives or novel forms of cooperation to address the challenges outlined above. FIC is a prospective venue for a deepened cross-sectoral analysis of benefits or drawbacks of policy options. These include loan guarantees to assure markets for selected products; "front-end" funding of product development with the expectation of subsidized pricing for resulting products; extended patents for selected products; compensation schemes to reduce liability exposure; tiered-pricing to subsidize procurements of vaccines; public-private ventures to prepare risk/benefit analyses of potential markets in support of product development; and legislative remedies such as tax credit incentives to defray R&D costs analogous to the Orphan Drug Act.

- **Creative Financing Schemes**

The launch of the *Heavily Indebted Poor Countries Initiative* represents a major departure in confronting debt problems of low-income countries and has created an unprecedented climate for converting debt to social investment. In support of the ongoing international consultative process, FIC will explore US frameworks for building scientific capacity in low-income nations through debt conversion schemes. To cite one illustrative example, a potential financing scheme adapted by the private and public sector is the exchange of long-term debt for local currency directed towards local projects of public benefit. Since the mid-1980s, this scheme has been employed successfully to preserve threatened ecosystems or promote environmental programs in low- and middle-income nations. It may be a feasible means to co-finance cooperative programs in health research with low-income nations focusing on the transfer and adaptation of new technologies. In principle "health for debt swaps" could fund national endowments for sustained support of cooperative research programs in health (e.g., capital investments for infrastructure, clinical research training, cooperative protocols). Moreover, there is a foundation of public policy for these arrangements in the enactment of P.L. 480, which enabled India, Pakistan and other nations to convert debt accrued through purchase of U.S. commodities into an S&T fund. One benefit of debt swap schemes is that debtor nations become true financial partners, an essential attribute for cooperation on an equal footing, yet are not required to generate significant new capital.

Policy Development Goals

- *In coordination with NIH's Office of Technology Transfer, examine incentives and disincentives for industrial investment in medical products of primary benefit to developing nations. This may entail a deepened empirical review of proposed incentive structures in consultation with industry.*

- *In coordination with relevant international organizations, examine creative methods of leveraging new resources for global health research through debt conversion or other schemes in support of the Heavily Indebted Poor Countries Initiative. This may entail a*

review of legislative precedents and previous Federal programs that might serve as suggestive models.

X . PUBLIC OUTREACH

NIH's international research activities ultimately depend on public understanding and support. The interdependence of nations in health and the benefits of international scientific cooperation need to be communicated thoughtfully to the public and legislature. This is especially important when competing economic demands prompt more insular perspectives and national self-interest is defined narrowly.

Applying the knowledge generated by NIH research to extend healthy life and reduce the burdens of illness and disability requires optimal communications. FIC is committed to communicating effectively with many groups on global health issues: scientists engaged in biomedical research; health care practitioners of all types; patients; members of the general public; the media; and the Congress. One objective is to strive to ensure that biomedical research as well as international health policies, practices and health news coverage are based on the best scientific information available. It is also important that FIC be seen as a credible, accessible resource for information on global health issues. Well-designed programs of information and outreach contribute to the perception of FIC as a valuable public resource. An enhanced communications program will provide valuable information to the international community on health choices, inspire young people to enter research careers in global health areas, and elevate the scientific literacy of the general public.

Program Development Priorities

- *Develop a coordinated communications strategy that includes FIC grantee institutions and relevant international organizations in a public outreach network.*

- *Target increased coverage of FIC programs across the nation, emphasizing mid-sized city media markets and background programs for regional reporters.*

- *Improve access to current research and clinical updates for scientists and health care professionals in low- and middle-income nation.*

- *Select and emphasize specific themes for maximum coverage on a rotating basis (i.e., emerging infectious diseases, bioethics, biodiversity, AIDS prevention), using the themes to write a range of feature articles, letters to the editor, op-ed pieces, etc.*

- *Develop a working rapport with "gateway" audiences (i.e., key journalists), especially those with an interest in NIH activities, science, professional and academic organizations.*

- *Explore the role of media in promoting global health literacy and affecting behaviors. This might take the form of colloquia on topical international issues in biology and medicine (e.g., origin of HIV) and the responsibilities of the media.*

- *Initiate fellowships in science journalism directed at low- and middle-income nations on the model of the Nieman fellowships sponsored by the Kennedy School of Government.*

FIC RESEARCH AND TRAINING OPPORTUNITIES

Training Grants

AIDS International and Research Program

International Training and Research Program in Environmental and Occupational Health

International Training and Research Program in Population and Health

Minority International Research Training Grant

International Training and Research Program in Emerging Infectious Diseases

FIC-NLM International Training Program in Medical Informatics

Tuberculosis International Training and Research Program

Actions for Building Capacity in Support of ICIDR Program

International Maternal and Child Health Research Program

Research Grants

Ecology of Infectious Diseases

Fogarty International Research Collaboration Award

HIV-AIDS and Related Illnesses Collaboration Award

International Cooperative Biodiversity Groups

Fellowships

International Research Scientist Development Award for U.S. Postdoctoral Scientists

Senior International Fellowship

Foreign-Funded Fellowship Programs