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Notes of Preparation

This proceedings document was compiled from written and audio-taped notes of the conference sessions and from printed texts submitted by session presenters and coordinators of discussion sessions. Wherever possible, for accuracy, the available printed texts were given precedence over written or audio-taped notes. In both cases, the presentations appearing in this document have been edited for clarity.

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CONTENTS

Session IV: Clinical Research Systems Compared

Session V: Differences in Chinese and U.S. IPR and Bioethics Systems

PREFACE

U.S. - CHINA COOPERATION PROGRAM IN SCIENCE POLICY, RESEARCH, AND EDUCATION

The U.S. - China Cooperation Program in Science Policy, Research, and Education is a decade-long initiative built on the experience gained from more than twenty years of cooperation in science and engineering between the United States and the People's Republic of China. The productive, long-standing relationship between the National Science Foundation (NSF) in the U.S. and the National Natural Science Foundation of China (NSFC) is a cornerstone of this cooperation. Additional information and links regarding this program can be found at:
<http://techcenter.gmu.edu/programs/science_trade_policy/us_china.html>

This forum is the second in a projected decade-long series of dialogues between representatives from the principal sectors of the science and technology (S&T) enterprise in each of the two countries. The first was held October 24-27, 1999 in Beijing, People's Republic of China. That meeting, addressing issues with significant implications for the vitality of science and engineering in the increasingly borderless, knowledge-based global economy, was an auspicious beginning. The summary of the proceedings of the first event can be found at: <http://www.twics.com/~nsftokyo/rm00-01.html>.

This second event, addressing Biotechnology and Biomedicine, was held December 4-5, 2000 at the National Institutes of Health, near Washington, DC in the United States. The Executive Summary and Report of Forum Sessions below provide a snapshot of the forum as well as a summary record of the presentations and discussions.

I. EXECUTIVE SUMMARY

Biotechnology and biomedicine were chosen as topics for the second activity in the decade-long U.S.-China science policy dialogues, especially because of the rapid advances taking place in research and applications. The goals in convening this forum were to insure that the voices and opinions of the best scientists of the two countries would become part of the public record with regard to key policy issues raised by these advances and to seek opportunities for expansion of cooperation in biomedical research and biotechnology between the two countries.

The forum was divided into two parts, the first dealing with research opportunities, and the second with challenges posed to scientific cooperation. These come about because of differences in our systems for assuring ethical research and the protection of intellectual property. Topics of discussion in Part 1 included:

1. Areas That Offer Mutual Advantages for Collaboration
2. New Technologies Providing Opportunities for Cooperation
3. Biotechnology and Ecology of Infectious Diseases
4. Clinical Research systems Compared
5. Differences in IPR and Bioethics Systems of China and of the United States

PART ONE: OPPORTUNITIES FOR RESEARCH COLLABORATION

The sessions of Part 1 began with descriptions of each country's organization, structure, and funding of biotechnology and biomedical research. The corresponding national organizations are the National Natural Sciences Foundation of China (NSFC) and the National Science Foundation (NSF) and National Institutes of Health (NIH) of the United States.

1. Areas that Offer Mutual Advantages for Collaboration. Drug Research Strategic Priorities. After a review of recent drug research in China, research in the future is to be directed toward the following strategic priorities. First, are the needs of social development. While the disease spectrum has changed in China, as it has in developed countries, the vastness of China and its population along with the differences among China's different regions mean that different kinds of diseases will co-exist for a time.

Second, China aims to contribute to the advancement of learning, especially in molecular biology and neurobiology. The timely exploration of drug genomics will be pursued into the post-genomic era, based on structural genomics and the developments from functional genomics to disease genomics.

Third, China aims to utilize fully the achievements of new high technology (e.g. computer-assisted drug design, combinatorial chemistry, new group screening). As part of this effort, China has established implementation programs including those addressed to improving research on traditional Chinese medicine in order gradually to modernize Chinese drugs. This program involves introduction of international standards into

substantive work to ensure high quality green medicinal material. It also involves implementation by the U.S. of administrative and regulatory standards such as the development of modern dosage forms and application of the General System of Preferences (GSP) applying to taxes and tariffs. The first targets will be development of complex prescriptions of Chinese drugs for diseases intractable to Western medicine. This will be oriented toward harmonization of the traditional Chinese holistic approach of using complex prescriptions for multiple targets in contrast with the tendency of Western drugs to focus selectively on a single target.

2. Technologies and Research Tools. Three new technologies or research tools were discussed with reference to facilitation of research: information technologies (IT), human genomics, and plant genomics. The Chinese presenter used telemedicine as an example of IT and illustrated by real-time and non-real-time diagnosis and consultation, on-line publication, and e-learning (or distance education). The U.S. presenter discussed five new information technologies (enhanced data acquisition, communications and networking, advanced application, data archives, and tools for knowledge generation and dissemination) with specific reference to the understanding of bio-complexity in the environment.

Human Genomics as a technology or tool for research was discussed by presenters from both China and the U.S. through reviews of each country's programs. The U.S. presentation noted that at lease five percent of the funding for the Human Genome Project in the United States goes to studies and research of ethical aspects.

Plant genomics as a technology or tool for research was also discussed. The Chinese presenter reviewed present and prospective research in rice genomics. The U.S. presenter spoke about nutritional genomics – the use of plants to improve human health – via enhancement of nutrition. In her talk, she referred to Golden Rice, a transgenic phenomenon that enriches the beta-carotene in rice, featured as a cover story in Time Magazine (Vol. 156, No. 5, July 31, 2000) to illustrate the concept of nutritional genomics as well as the popular interest in it.

3. Biodiversity and Ecology of Infectious Diseases. Biodiversity is a global concern and is generating international conventions and bilateral and multilateral environmental treaties, including the Convention on Biological Diversity, Convention on International Trade in Endangered Species (CITES), and the Ramsa treaty.

The biodiversity presentations addressed the importance of non-human biodiversity to human health in the four areas of (1) drug discovery from natural products, (2) biology of disease vectors, (3) biological indicators of environmental quality, and (4) use of non-traditional organisms to model human systems. All appear to be subjects of increased academic or industrial sectors in the United States and in China. This perspective was elaborated by examples and case studies including a review of China's R&D for the conservation of several of the endangered species with habitats in China and work on gene transfer and biosafety as presented in a review of transgenic fish R&D and related to biosafety principles published by OECD in 1993. A U.S. presenter discussed the

chemistry of biotic interaction to illustrate scientific benefits of studying the chemistry associated with biodiversity.

The U.S. presenter described the initiation of an interdisciplinary program on the Ecology of Infectious Diseases engaging ecologists, epidemiologists, and biomedical scientists. This interdisciplinary program addresses the challenge to science to probe the likely ecological relationships between, on the one hand, the unprecedented global rates of change of ecosystems due to biodiversity loss, and on the other hand the emergence of infectious diseases. There have been parallel advances in ecological science and biomedical research, but the relationships among these advances offer opportunities for exploration leading to deeper understanding. A review of AIDS research in China also demonstrated the nature and effectiveness of this interdisciplinary program and its potential with respect to China-US scientific collaboration.

4. Comparison of Clinical Research Systems of China and the United States. An overview of some features of China's clinical research system was part of the discussion of the Telemedicine program. Added to that was a presentation on cancer research. An outline of present status and further research plans, including better integration between traditional Chinese medicine and Western medicines was included in the presentation. The American participants discussed issues of the Organization and Management of Clinical Research at NIH, including design, monitoring, reporting, and oversight. Data and Safety Monitoring Boards (DSMBs) – to monitor patient safety and required for clinical trials – were highlighted in this review. DSMBs are mandated for appropriate oversight and monitoring particularly for multi-site clinical trials, in addition to the Institutional Review Boards (IRBs) for each site. China is familiar with and extensively uses Institutional Review Boards (IRBs), but the DSMB is not a well-implemented function in some research institutes in the current Chinese system.

5. IPR and Bioethics. On Intellectual Property Rights (IPR), China is undertaking its international obligations regarding IPR – including copyright, trademarks, and patents -- as part of its ongoing reform policy. It recognizes that the level of IPR protection is lower in China than in developed countries, but progress is being made. Participants described the current Chinese IPR system that China has built up was described, identified the IPR problems in biomedicine and biotechnology were identified, and discussed newly emerging problems (e.g. WTO participation).

IPR in the U.S. was reviewed in terms of Technology Transfer at NIH describing the development and implementation of the system used in the U.S. The review began with technology transfer legislation (e.g. Stevenson-Wydler Act) and its implementation in the 1980s and moved to its refinement in the 1990s. Goals of Technology Transfer, licensing terms, patents, examples of executed licenses, and royalties were discussed and illustrated (e.g. via Cooperative Research and Development Agreements – CRADAS, and Materials Transfer Agreement – MTA).

On bioethics, Guidelines on Ethical Review of Medical Research were published in China in 1998. The Guidelines address such concerns as conflicts of interest, scientific

integrity, risk and benefits of randomized trials, genetic markers of cancer risk and notification, employment, and health insurance. Four principles of bioethics are involved – beneficence, non-malfeasance, justice, and respect for autonomy of persons. Qualitative methods of presentation are used rather than quantitative. Protecting privacy and equal treatment are requirements. Adequate health care and compensation for participants in research are also strongly recommended.

The US emphasis at the forum built on the current status of bioethics guidelines and implementation. The presentation emphasized the extensive funding allocated to studies and research related to bioethics and activity in a global arena. The work of the National Bioethics Advisory Commission (NBAC) was discussed particularly with respect to new concerns. Bioethics has always been understood to be involved in the protection of individuals in clinical trials. But now, there is growing concern about biological material — blood samples, biopsy materials, slides, and survey data. An important challenge to bioethics research is illuminating the issues involved when the individual source is not present and may be far away or from a different nation.

The NBAC also called a global summit of national bioethics commission to promote dialogue about ethical issues that arise in research. There are national commissions in 38 countries so far and two international meetings have taken place in London and Tokyo, respectively. All recognize that the aim is harmonization and collaboration – there is no single set of guidelines that can be agreed upon by every nation in the world. This situation is recognized not as a barrier to collaboration, but an opportunity to use collaborative activities themselves to identify areas where there are difficulties that need to be worked through.

The distinction between process and substance in bioethics was emphasized. Informed consent, for example, may be thought of as a process and involving distinctions like signed consent versus proxy consent. On the substantive side, there are all kinds of creative ways of implementing the process, but the overarching issue must focus on respect for the person to assure a genuine willingness and voluntariness for people to allow things to be done that they might not ordinarily allow.

PART 2: DISCUSSION OF ISSUES AND DIFERENCES

Frank discussion of such socially difficult subjects such as AIDS in both countries was matched by equally frank discussion of differences in clinical approaches to drug testing, human subjects protection and ownership of, and therefore profitability from, basic biological substances. There were two Small Group Discussions reporting in the Plenary Session. The report on the discussion of Biodiversity and Intellectual Property Rights presented the following issues identified in the group discussion as policy challenges to collaborative research:

1. Differences between U.S. and China policies on what constitutes a patentable invention.
2. Costs of patent prosecution and maintenance are prohibitively high.

3. Lack of legal clarity and/or consensus among scientists regarding shared rights in a collaborative research project.
4. Access to biological materials is complicated by unclear and developing regulations restricting their transfer and the absence of clear standards for informed consent and for compensation.
5. While the principle of special rights of indigenous peoples to biodiversity is widely recognized, in practice it is difficult to define the individuals, communities, organizations or tribes to whom these rights accrue.
6. The increasing probability of commercialized outcomes from a research project may already be inhibiting basic science in some cases. Proprietary interests in research products are in some cases slowing access to samples, sharing of data, and publication of results.

Some guidelines for cooperation that were suggested by the Chinese delegation and widely supported:
1) Equity and voluntarity in design of project
2) Mutual benefit
3) Mutual participation
4) Equitable sharing of benefits
5) Mutual ownership of patents

The second group report on bioethics agreed with the views of the first report that many of the issues being raised go far beyond the responsibilities of this particular forum. However, it is important to signal from the perspective of the scientific community our concerns and interests in the issue of intellectual property, from both the perspective of the protection of intellectual activity and stimulation of international research, and also our concerns and interests about the ultimate accessibility of the product of that research to the population in need of new medicine, new medical technology and all the fruits of biomedical research. It was agreed that the record of this meeting should reflect the concern and interest of the scientific community. The group did not recommend specific proposals for reform, but identified the following issues.

1. Recruitment of participants as a bioethical policy challenge, especially in three areas: HIV-AIDS, cancer, and drug abuse.
2. Disclosure of information in public health, distinguishing between those issues important for disclosing to individuals about their own risk-taking behaviors and the information that is needed in order to protect them from the reactions of the community. This issue has two components — medical records and privacy.
3. What to do when a study provides useful information and potentially even a useful product, including whether there is a responsibility to provide the "study benefit" to individuals, communities, or countries.
4. Whether, as a policy, the focus should be on the low-technology alternative as it may not be realistic to study and test a very expensive drug or intervention that has no chance of becoming available due to cost.
5. Establishing Data Safety and Monitoring Boards and insuring their expertise. It is doubtful that a local committee in a small community will have as much expertise as a

larger national committee that can review multi-center studies. The issue then, is how to address levels of expertise necessary in oversight of international or bi-national research including the ethics committees themselves, the investigators, and the research participants.

II. REPORT OF FORUM SESSIONS

The goals in convening this forum were to insure that the voices and opinions of the best scientists of the two countries would become part of the public record with regard to key policy issues raised by these advances and to seek opportunities for expansion of cooperation in biomedical research and biotechnology between the two countries.

These goals were addressed through a review of:

- **Research opportunities and cooperative research**: areas at the frontiers of biotechnology and biomedicine where collaborations offer promise to extend our capacity for discovery and examine factors that have historically have helped collaborations between China and the US be successful, and

- **Challenges:** common features and the differences of our systems for assurance of ethical research and the protection of intellectual property.

These issues were addressed in two parts of the Forum: Part One comprised five sessions of presentations by participants from both countries focused on the first bullet above. Part Two reports on the session that focused on the second bullet. The following is an account of the information delivered and exchanged, organized in the sequence in which the sessions occurred.

PART ONE: RESEARCH OPPORTUNITIES

Session I. Areas that Offer Mutual Advantages for Cooperation

Five papers were presented in this session:

- "An overview of funding for biomedical research in China in the Department of Life Sciences," NSFC by Xinsheng Ye
- "Present situation of new drug research in China," by Bo Yi Qin
- "Acupuncture: from pain relief to treatment of drug addiction," by Ji-Sheng Han
- "Establishing successful research collaborations," by Roger Detels
- "NCI intramural experience in collaborative cancer prevention research in China," by Philip Taylor.

The paper by Xinsheng YE provided an overview of the organization and structure for funding biomedical research in China. The National Natural Science Foundation of China (NSFC) is a government agency established in 1986. As with the National Science Foundation (NSF) in the U.S., NSFC does not perform research but directs, coordinates, and finances basic research and some aspects of applied research, identifies and trains research talent, and promotes the advancement of science and technology for economic and social development. NSFC is composed of seven academic departments plus bureaus and an administrative office. The Department of Life Sciences is the largest department

and is subdivided into three sections: biology, basic medicine, and basic agriculture. [See http://www.nsfc.gov.cn].

The NSFC budget has been increasing rapidly from 80 million yuan RMB in 1986 to 13 billion yuan RMB in 2000 (about the equivalent of 1.6 billion US dollars at the exchange rate of 0.121 USD per China Yuan RMB). Projects fall into three categories: general, key, and major. The general category includes investigator-initiated projects, projects for young scientists, and projects for developing regions. These projects each have an average funding level of about 180,000 yuan RMB (about $22,000 dollars US). The Department of Life Sciences funding pattern from 1996 to 1999 is shown in Table 1.

Table 1
Department of Life Sciences, NSFC
Funding Pattern, 1996-1999

Project Category	Number of Projects	Total Budget
General	16,027	10 billion yuan RMB
Key	153	127.8 million yuan RMB
Major	78	78 million yuan RMB

The research emphases among these projects included immunology, cancer (or oncology), neuroscience, traditional Chinese medicine, post-genomics, and research on infectious diseases.

With the completion of human genome sequencing, the biomedical sciences are at the threshold of extraordinary advancement. Genomic research will have great impact on research on diseases and human health. Accordingly, the NSFC's Department of Life Sciences will place an even higher value on biomedical research and provide encouragement to projects employing novel concepts, approaches, or methodology; projects making use of the advantages and resources of China, and projects integrating biomedical research with research in other disciplines such as mathematics, physics, and material sciences.

Bo Yi Qin’s paper described the present situation of new drug research in China. New drug research in China has a long history and this is a favorable time for research in China. Ranks of professionals, integrated branches of learning, and supporting resources have been developed to a high level of excellence. In the last fifty years, many kinds of new and inventive drugs have been approved for marketing in China including recent success in treating leukemia with arsenides. Also, there has been repaid progress over the last fifteen years in the production of drugs by biological methods. These include success in the development of genetic recombinant human growth hormone and eleven kinds of drugs produced by genetic engineering that have been approved for marketing. Eight other such preparations have been included in the pharmacopoeia of the People's Republic of China and another fourteen are in the clinical trial stage.

Thus, China is in the position of applying achievements in biomedical research relatively quickly to medical care. For example, mortality data have shifted. Where infectious

disease was the leading cause of death in the 1950s, it is now tenth. The mortality of cardiovascular disease declined from 40 percent in the 1970s to about 10 percent at present. The five-year cure rate for cancers has reached 39.1 percent. The endemic disease that were seriously harmful in the past — schistosomiasis, kalaazar, filariasis, endemic goiter, and Ke-shan — have been controlled. The comprehensive impact of these achievements is reflected in the lengthening of life span from 35 years in the 1950s to more than 70 years today. At the same time, China is in a better position to put more human and financial resources into research on new drugs to achieve even greater results along three dimensions.

First, China is addressing the needs of social development. In China, the disease spectrum is changing as in developed countries. But because of China's vast territory and the large cultural differences among different regions, the changes in the disease spectrum are not uniform and different kinds of diseases will co-exist for a time. This requires that we continue to study drugs for prevention and treatment of various infectious diseases, especially the anti-tuberculosis and anti-AIDS drugs, and for various heart, brain, and diabetic diseases. Additionally, prevention and treatment of various mental diseases (such as neurasthenia, anxiety, depression, sever psychosis, behavior problems in children, alcohol and drug abuse, senile mental diseases, and suicide in students) will require continuing attention.

Second, there is an effort to follow the advancement of the forward branches of research, especially molecular biology and neurobiology. As the post-genome era is approached, China plans to carry out the timely exploration of drug genomics, based on structural genomics and developments from functional and disease genomics.

Third, there shall be full exploitation of the potential of new high technology. New technologies such as computer-assisted drug design, combinatorial chemistry, group and high throughput screening, have been established in some laboratories in China for research and development of new drugs.

Simultaneously, there are plans to improve research on traditional Chinese medicine through the full utilization of new technologies and gradually modernize Chinese drugs. The strategy to be implemented is first, to introduce international standards into a series of activities such as ensuring high quality green (natural) medicinal material, implementation of the GAP system, and development of modern dosage forms. The plan is to start with intractable diseases and develop the typically complex prescription of Chinese drugs shown to be effective for diseases that cannot be treated with Western medicine. There is often not a set treatment for certain intractable diseases with Western drugs because the mechanisms of the diseases are unclear. However, Chinese can be used for treatment base on the overall analysis of symptoms and signs, while they are obviously present, without knowing the mechanism clearly. It is difficult to screen Western drugs when there is no animal model as is usually the case for intractable diseases, while Chinese drugs can be tried directly on the human patient without an animal model.

Moreover, Western drugs usually focus selectively on a single target while drugs for intractable conditions are often related to multiple pathological changes. The complex prescriptions of Chinese drugs may be effective because most of them act on multiple targets. Cats are considered good cats if they catch rats regardless of whether they are black or white. Above all the factors that may be involved, therapeutic efficacy is first. Chinese drugs have promising prospects if they can be modernized in accord with international standards.

Thus, Research on new drugs is an important area for collaboration of China with American colleagues. China has both a long history to use for reference and support by modern medical theories and technology. With rich medicinal resources and high quality professionals in China, we believe that collaboration with scientists from various countries can push drug research and development to new levels of brilliance and achievement.

The paper of Ji-Sheng Han discussed research on acupuncture for pain relief and treatment of drug addiction. Acupuncture, as a part of China's traditional health care system can be traced back for at least 2,500 years. The ancient technique of inserting a metallic needle into the skin and manipulating it has now been largely replaced by *electroacupucture* (EA), electric stimulation applied on the needle in a device called *Han's Acupoint Nerve Stimulator* (HANS). This presentation cited tests that show HANS treatment to be an effective analgesic for low back pain, migraine, muscle spasm and other conditions causing pain. EA is capable of mobilizing opiate-like substances in the brain (e.g. encephalin, endorphin, endomorphin, and dynoprin. However, use of EA for extended time or frequency, leads to the production of anti-opiate substances in the brain. Thus, the overall efficacy of EA depends on the relative balance between the opioid and anti-opioid.

EA has been used, over the last decade, for the treatment of heroin addicts. Animal and human studies reveal that high frequency (100Hz) EA suppresses the withdrawal syndrome, while low frequency (2 Hz) EA reduces craving. EA is associated with a temporary abstinence during the detoxification period, but 95 percent or more of patients go back to drug use within a month. Some sort of portable HANS for self-administration may open the way to a new non-pharmacological treatment for drug abuse.

Roger Detels' paper discussed factors involved in establishing successful research collaborations. This paper identified two kinds of considerations for successful collaborations. One involves substantive areas — areas of research and research support. The other concerns tangible and intangible factors as keys to successful collaboration. He identified six areas as promising for research and research support collaboration:

- Determination of prevalence and correlates (risk factors) for specific diseases,
- Intervention studies. (for example treatments, vaccines, reducing risk activities, and mobilizing community action),
- Elucidation of biological mechanisms (molecular, genetic, clinical),
- Resource building (e.g., laboratory resources, clinical skills),

- Manpower development (training), and,
- Workshops (technical skills building, policy coordination).

Direct and Tangible Factors include:

- Priority and relevance for host country.
- Clear lines of responsibility and authority.
- Mutually agreeable policy on publications, patents, etc.

Other, somewhat intangible factors include:

- Trust and frank communication.
- Identified mutual benefits to both parties.
- Cultural sensitivity and awareness.
- Respect for local requirements and regulations.
- Understanding of needs of individual investigators.
- A 'savvy' collaborator. ('Savvy' is an American slang expression referring to a person who has practical understanding or knowledge.)

Philip Taylor's paper reported on his experience, from the point of view of the National Cancer Institute of NIH, in collaborative cancer prevention research in China. This presentation considered two examples of studies in China: nutrition intervention trials and a study of early detection of esophageal cancer, both in Linxian. The China collaborator is Dr. You-Lin QIAO, who will report on ethical issues in conducting cancer epidemiological studies raised in this collaboration as part of Session V. Details of the techniques and data are found in the paper. The issues raised by these experiences were grouped into four categories.

- Unique Opportunities (e.g. high population rated, unique cancer types)
- Generalizability to the U.S. (recurring question of relevance of research in China to the U.S. population).
- Barriers (physical, regulatory, cultural, infrastructural), and
- Intellectual Property Rights.

Several of these issues were discussed further in other sessions.

Session II. New Technologies that May Provide Opportunities for Cooperation. (Information Technologies, Human Genomics, and Plant Genomics).

Six papers were presented in this session — two, respectively, for each of three technology categories — Information Technology, Human Genomics, and Plant Genomics:

- "Telemedicine in China," by Xiaomin Wang.
- "Technologies for understanding biocomplexity in the environment," by William Michener.
- "The human genome project in China," by Zhu Chen
- "The human genome project in the U.S.," by Elke Jordan.
- "What we achieved and plan to do in rice genomics as a cereal model," by Guofan Hong.
- "Nutritional genomics - manipulating plants to improve human health," by Mary Lou Guerinot.

In the realm of Information Technologies, Xiao-Min Wang discussed telemedicine in China — the use of IT in health care. This endeavor is organized under the China Golden Health Network (CGHN) project, begun in 1995. This project links China's hospitals to share resources and experience for patients anywhere in China. CGHN provides telediagnosis, teleconsultation, and distance education via the specialized Satellite Network linked to the ground network. The China Telemedicine Journal is a part of the CGHN project that facilitates dissemination and effective use of the IT capabilities. Dr. WANG discussed several cases, the use of the network for distance education, and the accomplishments of the CGHN project. CGHN can be accessed on the Internet at http://www.2919.net/jw/english/

William K. Michener discussed IT-related technologies for understanding biocomplexity. The following abstract of his paper summarizes his presentation

At least five related technologies are contributing to our understanding of biocomplexity in the environment. These include:

(1) New or enhanced data acquisition technologies;
(2) Communications and networking;
(3) Advanced applications;
(4) Data archives; and
(5) Tools for knowledge generation and dissemination.

Massive data streams are resulting from new and miniaturized *in situ* sensors, global remote sensing efforts (e.g., the Global Terrestrial Observing System), and hyperspectral sensors. Wireless technologies play an increasingly important role in communicating *in situ* sensor data from remote locations, greatly enhancing our ability to “instrument the environment.” Extensive high performance networks such as Internet 2 and STAR-TAP are now available and are contributing to the exchange of data and models, as well as

intersite to international scientific collaboration. Increasingly, environmental science is conducted over the Internet and new, advanced applications are emerging.

Examples of the types of applications that will enable us to better understand biocomplexity include new collaborative visual environments (e.g., CAVE), the Collaboratory for Microscopic Digital Anatomy (i.e., Web-based telemicroscopy), and biodiversity workbenches (e.g., Species Analyst). Data archives are beginning to be fully incorporated into the environmental sciences. New software that facilitates data management for ecologists as well as serving as a front-end to a data archive facility is near completion as part of the Knowledge Network for Biodiversity.

Metadata clearinghouses are increasingly used for data discovery and documentation purposes. Finally, Web portals and the Access Grid are changing the ways we perform science by greatly enhancing our ability to rapidly generate and disseminate knowledge. These five technologies will support ecologists and other biologists as they continue to expand their scientific worldview (spatially, temporally, and thematically) and address mechanisms underlying biocomplexity in the environment. Some key future challenges include: lack of communication and networking infrastructure in many areas, bandwidth limitations, lack of training in emerging technologies, and need for international standards (e.g., metadata standards, data compatibility, etc.)

Zhu Chen of China discussed the Human Genome project in China. China is the most populated country in the world (accounting for 22% of world's total) and the Chinese population is composed of many ethnic groups which represents a precious genetic resource for studies on human genome diversity and evolution, as well as for hunting of human disease related genes. The Human Genome Project (HGP) in China was launched in 1994, and has been supported by the National Natural Science Foundation of China (NSFC), the Chinese High Tech Program, and the National Key Research Program.

China presents both genetic diversity and large populations that are genetically isolated. Thus, China offers unique potential for the advancement of studies of gene mapping and functions. The paper reported on a study on the genetic relationships among 30 ethnic groups in South and North China and the results were compared with 15 reference populations in the world. It was found through this study that Chinese population could be divided into Southern and Northern ones, that the two populations may originate from the South and that the gene pool of East-Asian population is likely to be derived from Africa. The study on disease genes has also made some progress and specific examples were discussed. Also, an initiative has also been made in the mapping of polygenic disease loci. In addition, several groups have made breakthrough in large scale cloning of human functional genes.

Dr. Chen discussed other aspects of the sequencing of human genomic DNA. In closing his presentations, he asserted that the Human Genome Project in China should be more integrated into the international efforts and that mutually beneficial collaborations will be further promoted.

Elke Jordan discussed the Human Genome project in the U.S. as part of the Human Genome Project (HGP) as an international research effort to characterize the genomes of human and selected model organisms through complete mapping and sequencing of their DNA, to:

- develop technologies for genomic analysis,
- examine the ethical, legal, and social implications of human genetics research, and
- train scientists who will be able to utilize the the tools and resources developed through the HGP to pursue biological studies that will improve human health.

Dr. Jordan described the initial research plan of the U.S. for the first five years (1990-1995) of what was then projected to be a fifteen-year research project and focused the efforts of the research community on the most important initial objectives. Because progress was more rapid than anticipated, the 1990 plan was updated in 1993 by extending the initial goals and scope of genome research. The new goals were publicly presented in an article in Science (Science 262:43-46;1993). These goals were also a joint NIH-DOE effort and covered Fiscal Years 1994-1998.

In 1998 another NIH-DOE 5-year plan was developed to cover completion of the original objectives of sequencing the human genome and to expand the HGP to the study of genetic variation and functional analysis of the genome. This plan was also published in Science. (Science. 282: 682-689; October 23, 1998.)

The National Human Genome Research Institute (NHGRI) supports research projects aimed at accomplishing the goals of the HGP at universities and research institutions across the U.S. The development and management of these projects is carried out by the NHGRI's Division of Extramural Research (DER). The DER, with advice from the extramural research community and the National Advisory Council for Human Genome Research, sets the scientific priorities for HGP research and supports and manages the peer reviewed research projects that address these priorities.

Dr. Jordan emphasized that significant effort the U.S. has made from the outset to support research on ethics. The Ethical, Legal, and Social Implications of Human Genetics Research Program (ELSI) at NIH was established in 1990 by the architects of the Human Genome Project to anticipate and address the ethical, legal and social issues that arise as the result of human genetic research. The "working draft" sequence is to be published in February 2001.

For the future. the U.S. program will continue addressing the goals in the aforementioned five-year plans. Two receiving attention are the following. One is to continue sequencing selected model organisms. The mouse genome is next on the list. The rat genome has been studied. The second is developing bioinformatic tools and computational strategies for the collection, analysis, annotation, and storage of the ever-increasing amounts of DNA mapping and gene expressing data.

Turning to Plant Genetics, Guo Fan Hong presented a paper on what China has achieved and plan to do in rice genomics as cereal model plant. He discussed the structural genomics of rice and the functional genomics of important agronomic traits in rice. Genes essential for agronomic performances of crops can be utilized to further benefit food production and quality through genetic engineering. In this program, genes related to flowering, plant architecture, fertility, reproduction and metabolic controls in rice will be identified through a combinatorial approach of genetics, molecular biology and functional genomics. Two major aspects of this program are mutant screening and identification and gene isolation using high throughput technology. Both EMS-induced and insertional mutants by transposons and T-DNA will be produced at a large scale. To isolate as many genes as possible, gene expressional profiles will be established and compared by microarray technology. In this way, key agronomic genes controlling the quantity and quality of rice grains will be tracked down.

His paper addressed several aspects of such topics as:

- Research targets for the next five years.
- Recent results, and
- International collaborations.

Mary Lou Guerinot discussed field of Nutritional Genomics — manipulating plants to improve human health and works at the interface of plant chemistry, biochemistry, genomics and human nutrition. Plant foods contain almost all the minerals and organic nutrients established as essential. The work of nutritional genomics can fortify foods before harvest with added nutrients. For these reasons, plant and nutritional genomics provide important opportunities for collaborative research.

An important issue involves crops that benefit the farmers that grow them, but, as such, do not offer added value for the people who consume them. The challenge is to add nutritional value for consumers. This is a matter of balancing input traits versus output traits of plants. One example involves the production of rice grains containing beta-carotene. This could improve Vitamin A nutrition and prevent between 1 and 2 million deaths each year among children aged 1-4 years. Beta carotene enriched rice, called Golden Rice, was featured as cover-story in Time Magazine (issue of July 13, 2000). Golden Rice is a transgenic phenomenon with the gene of a butterfly inserted into rice. It enriches the beta carotene, in rice, that is transformed into Vitamin A by humans.

An important research issue in plant genomics from the point of view of enhanced nutrition is to understand how plants acquire minerals. Dr Guerinot identified several areas of understanding that can come out of such research. This can lead to improved plant growth and crop yields. It can also improve animal and human nutrition and address problems of malnutrition. This knowledge can also lead to better utilization of marginal soils and soil remediation. As an example, iron in plants is an important issue. Iron deficiency is the most common human nutritional disorder and most people get their iron from plants. Yet, iron is one of the three nutrients that most commonly limit plant growth. Also, certain plants naturally hyperaccumulate selenium, which has anti-

carcinogenic properties. Plant genomics also offers the potential of producing edible vaccines.

But along with the promise of plant genomics, there are some problems. Such activity may introduce new allergens or exacerbate existing ones. Moreover, some vitamins and minerals have upper limits of safety, so the amounts consumed must be monitored carefully.

Another problem concerns patents and patent policy. There are about 70 different patents tied up in golden rice. That means anyone who wants to produce the seeds for crop development will have a very difficult time just assembling the necessary licenses from the extensive number of individuals or companies that hold the patents. There are also the ethical, legal, and social issues involved in deciding which foods to fortify, and who gets to decide.

Currently, the 2010 Project is a significant focus for plant genomics. The goal is to know the function of every one of the 25,000 genes in the *arabidopsis* genome by 2010.

Session III. Biodiversity and Ecology of Infectious Diseases.

Six papers were presented in this session — four addressing Biodiversity and two, Ecology of Infectious Diseases.

- "Wildlife conservation in China: policy practice, and prospects," by Zhigang Jiang and Keping Ma.
- "Biodiversity studies in China: progress and opportunities for cooperation," by Zuoyan Zhu.
- "Biodiversity and human health," by Joshua Rosenthal.
- "The chemistry of biotic interaction: can we benefit from studying the chemistry with which biodiversity provides us?," by Jerrold Meinwald.
- "Current AIDS research in China and potential for future AIDS vaccine collaboration for China and the U.S." by Yiming Shao.
- "Ecology of infectious diseases," by Joshua Rosenthal.

Zhi-Gang Jiang presented the paper co-authored with Ke-Ping MA on wildlife conservation in China. He pointed out the China is rich in biodiversity of its fauna and presented data on endemic species. The scope and diversity of endemic fauna arises significantly from China's size as does its human population. This combination puts enormous pressure on other resources that are limited. Nevertheless, China undertook reform and has made strides towards saving wildlife.

China is a party to many international conventions and bilateral treaties including the Convention on Biological Diversity, Convention on International Trade in Endangered Species, and the RAMSA treaty. But China lacks the financial and human resources to protect all habitats of species that need protection. This has led to the establishment of 14 wildlife rescue and breeding centers in 7 wildlife parks. By cooperation with foreign

colleagues, many rare and endangered species are surviving *ex situ* conservation. The U.S. has been engaged in the popular project with pandas.

China has also set up programs to compile biodiversity and endangered species inventories such as the *Red Data Books of Chinese Endangered Animals* and *Fauna Sinica*. The paper outlines policy, practice, problems, and prospects in China's wildlife conservation program and presents special cases.

Zuoyan Zhu presented a paper on gene transfer in fish and biosafety. He reported that based on the technique of microinjection, the first batch of GH-transgenic fish was produced in China and was established as a model of transgenic fish. The "all-fish" GH-transgenics not only grew faster but also were more efficient in utilizing dietary protein than the controls. Meanwhile, the transgenics had significantly higher body contents of dry matter and protein, but lower of lipid than those of the control. Sterile of triploid transgenic common carp were successfully produced, which are safe for the water-ecosystem. Tests with mice, fed with "all-fish" GH-transgenics or the control fish, respectively, showed no significant differences in physiological and pathological characteristics. The safety class of this "all-fish" gene-transferred common carp has been determined to be in the safest class (Level I) in terms of the biosafety equivalence system developed by OECD in 1993.

Joshua Rosenthal presented the paper, Biomedical Study of Biodiversity, starting with identification of four broad areas where non-human biodiversity is important to human health — drug discovery from natural products, biology of disease vectors, biological indicators of environmental quality, and numerous topics that use non-traditional organisms to model human systems. He provided an overview of the scope and breadth of the study of diversity of non-human bio-organisms and proportionate provided data on the contribution of natural products to four therapeutic areas in arguing that these medical areas benefit from an expanding knowledge base in the biodiversity sciences, and all appear to be experiencing increased interest from the academic or industrial sectors of the United States.

In addition to first-rate biomedical research, he argued that there are several important conditions that will enable advances in sustainable use of biodiversity in these areas. From a scientific standpoint, advances require excellent understanding of the systematics and taxonomic identity of organisms, as well as up to date knowledge of their geographical and ecological distributions. In addition, access for scientists to those studies and the resulting data are critical. He mentioned several global and regional initiatives, including Species 2000, Integrated Taxonomic Information System, and the Global Biodiversity Information Facility, that the U.S. supports to help link and verify taxonomic and inventory information on biodiversity.

He argued that the increasingly global nature of biomedicine and biodiversity research efforts requires that clear guidelines be developed for legal access to biological organisms, and mutual understandings regarding contributions to intellectual property and the sharing of benefits associated with their use and development.

Dr. Rosenthal then described the International Cooperative Biodiversity Groups program Involving three U.S. government agencies — the National Institutes of Health, the National Science Foundation and the Department of Agriculture. This included identification of the program's goals, the awards it has made, and the types of research it supports and the clear and enforceable guidelines for the treatment of intellectual property and equitable benefit-sharing.

Next, Jerrold Meinwald discussed the chemistry of biotic interaction in asking if we can benefit from studying the chemistry with which biodiversity provides us. Insects and related arthropods, arguably the most successful animals on earth, are especially adept in the exploitation of chemical mechanisms for such vital activities as attracting and selecting mates, locating food, defending themselves from predators, and a wide variety of other purposes. Elucidation of these defense and communication mechanisms provides deep insight into the emerging field of chemical ecology. It also provides opportunities for the development of new biorational techniques that could prove to be of enormous value in connection with the discovery of new drugs, the control of arthropod-borne diseases, the protection of forests, and the pursuit of sustainable agriculture. The exploitation of discoveries in these areas can, however, also raise perplexing questions in the area of intellectual property rights.

The first step for a chemist concerned with these endeavors is to fully characterize the molecular species responsible for the biotic interaction of interest. This area of natural products chemistry is often particularly challenging, because it is usually necessary to devise an appropriate bioassay by which an isolation scheme can be monitored. In addition, the fact that effective chemical signaling in nature may involve as few as hundreds of signal molecules, while chemists usually require many trillions (10^{12}) of molecules even to characterize known compounds, and much larger quantities to determine the structures and stereochemistry of novel structural types, places a premium on the development of nanomolar or even femtomolar separation and characterization techniques.

Because of the alarming rate of species loss worldwide, the need to study natural products chemistry is now greater than ever. A strong case can be made for the special benefits that can be expected from the establishment of international, interdisciplinary groups to pursue this work. Standing in the shadow of gigantic genomic and proteomic projects, however, natural products research is in danger of losing the modest support it now enjoys. The need for renewing interest in this area, as well as in the closely related discipline of chemical ecology, is urgent. Whether this urgency is perceived and acted upon at the highest policy-making levels worldwide will determine whether this uniquely important area of science will flourish or fade in the 21st century.

Joshua Rosenthal presented a second paper titled the Ecology of Infectious Diseases. This presentation was an extension of his earlier one in touching upon all four of the broad areas he identified in his earlier presentation where non-human biodiversity is important to human health. With regard to infectious diseases, he identified Malaria,

Leishmaniasis, Lyme disease, Hanta virus, and Cholera as examples of more than 35 infectious diseases that have emerged or reemerged around the world in the past 20 years. Simultaneous with this trend the world is seeing unprecedented rates of change in the environment and ecology of non-human biota on almost every continent. Virtually all of the world's terrestrial and aquatic communities and ecosystems have undergone dramatic changes due to biodiversity loss, global climate change and environmental contamination. The coincidence of broad scale environmental changes and emergence of infectious diseases may be accidental, but it appears likely that it in many cases that this coincidence reflects underlying ecological relationships. The role of biological diversity and habitat structure in stabilizing communities of plants, animals and microorganisms has received a great deal of attention from ecologists in recent years. As a result our understanding of the impact of various types of perturbation on ecosystems and our ability to model and predict those impacts has grown considerably. However, few of the related advances in ecological science have yet contributed to biomedical research and public health.

In a parallel fashion our understanding of proximate factors that contribute to disease transmission and host-pathogen interactions in the human body has grown tremendously in recent years with greater knowledge of the genetics of virulence and immunology. However, the link back to biotic systems that contribute to population dynamics of disease reservoirs and vectors remains poorly understood.

The National Institutes of Health and the National Science Foundation, in collaboration from the U.S. Geological Survey, the National Aeronautics and Space Agency, and the U.S. Department of Agriculture have initiated an interdisciplinary research program on the Ecology of Infectious Diseases. This program brings together ecologists, epidemiologists and biomedical scientists to elucidate the underlying biology of human-induced changes to the environment, including habitat conversion, climate change, invasion of exotic species, and chemical contamination that may affect disease prevalence in humans. One of these projects involves collaboration with scientists at the Langzhou Medical College, Xinjiang Medical University, and East China Normal University in Shanghai to study the dynamics of Human Alveolar Echinococcus in pastoral communities of West Central China.

Yiming Shao presented a paper on the topic of current AIDS research in China and potential for future AIDS vaccine collaboration for China and US. After going through the introducing phase in the middle 1980s and slow expansion stage in the early 1990s, the HIV/AIDS epidemic has entered a fast spreading stage in China since the middle 1990s. The estimated number of HIV infection has jumped from 10,000 in 1993 to more than 500,000 by 2000. Without vigorous control measures and swiftly implemented a comprehensive plan , the projected number of HIV infection could in China reach 10 million by 2010.

Chinese government has committed to lead a national campaign involving all sectors of the government and NGOs and mobilizing all aspects of the society to fight the AIDS epidemic. The overall strategy is to put the education first and to reduce the risk behavior

in the high-risk groups and to increase the general awareness of self-protection in the society. The social intervention approach is complemented and strongly supported by the biomedical intervention approaches including epidemic surveillance, molecular epidemiology, clinical research and vaccine development.

A sentinel surveillance networks involving more than one thousand HIV testing laboratories have been established in various regions of China. The networks have generated large quantity of epidemiological data useful for estimation and monitoring the epidemic. The national HIV molecular epidemiology survey found 7 subtypes of HIV-1 as well as HIV-2 and traced the spread of major strains in various regions of the country. The three major HIV-1 subtypes (B', C and B'/C recombinant) cover 80% people infected in China and therefore have been selected as the prototype of HIV vaccine stains. The full-length genome of the strains have been cloned and sequenced.

Three candidate HIV vaccines have been constructed from them, including virus like particle, DNA and live vector vaccines. The DNA vaccine constructed with synthetic gene technology has substantially improved its expression level in mammalian cells and got strong immune response in animals. The recombinant vaccinia virus vaccine containing HIV gag and env genes has also shown good immune response especially when used as a boost after DNA vaccine priming. The phase I clinical trial is under preparation and will start in one to two years depending on the time needed for approval by the State Drug Administration (SDA).

Through close collaboration between traditional and molecular virologist, a novel HIV vaccine has been designed based on the world's first lentivirus vaccine, the Equine Infectious Anemia Virus (EIAV). The EIAV vaccine has been developed and successfully used in China since early 1980s. Specific mutations are found present in the vaccine strains, but absent in the wild type strains of EIAV. These mutations affect the secondary structure as well as phosphorylatin and glycosylation of the critical antigens. The important information carried in the EIAV vaccine has been translated into the corresponding structure and property of HIV antigen. The protein engineering technique has been used to construct a new generation of HIV vaccines.

Most of the above progress in AIDS research has been made through close cooperation with international scientists, including the US colleagues. Being the largest developing and developed country in the world respectively, China and US not only shared the past collaborative experience, but also have great potential for its future expansion, especially in the AIDS vaccine field. The AIDS epidemic in the developed world is slowing down, but is still in its fast expanding phase in the developing countries. Considering the size of the cohorts needed to show a statistically significance, it becomes more difficult to evaluate low efficacy vaccines in a developed country, but much easier to do so in a developing country. Therefore, the close collaboration between them is crucial. The US has the state of the art technology to improve the design and upgrade the vaccine products. China has good infrastructure and professional teams experienced for clinical evaluation of vaccines. China is also capable of producing large quantity of cheap vaccines was proved successful in providing them to her huge population. A closer

collaboration between China and US in the AIDS vaccine field could greatly speed up the process to reach the ultimate goal of an effective and affordable AIDS vaccine for the whole world.

Session IV. Clinical Research Systems Compared.

Three papers were presented in this session:

- "Cancer research in China," by Yang Ke.
- "Organization and management of clinical research at NIH," by Richard Mowery.
- "Clinical trial oversight," by Belinda Seto.

Yang Ke presented a paper on cancer research in China. He began by discussing present circumstances that as a developing country with a large population, China is a nation of high cancer incidence. In the past decades, the government invested a great amount of funds, labor power and material resource to support cancer research, which has brought on some achievements in prevention, diagnosis and treatment, as well as the basic research in the field. The incidence and mortality of some tumors have decreased. However, with the industrialization and the rapid change of people's lifestyle, the incidence of some other tumors is increasing. The total mortality of cancer is still a leading cause of death. Cancer research remains a baffling medical problem, which needs continuing efforts at present and in a long period of time in the future. Extensive collaboration between Chinese scientists and researchers all over the world in this field should be able to make better contributions in the battle of conquering cancer. Dr. KE discussed five components of the effort being made in China.

The first component is the study of the characteristics of cancer incidence in China. Cancer is the most serious public health problem in this country. However, the disease and cause of death spectrums in this country have changed over the past twenty years with cardio-cerebro-vaso diseases, malignant tumors, and chronic non-communicable diseases now posing the main threat to people's lives and health. Dr. KE presented additional data on the changing composition of cancer in China

Besides the difference of the composition of cancer in this country, another important characteristic of cancer distribution is the existence of high incidence areas and high-risk populations. In the past several decades, Chinese scientists conducted many epidemiological researches and launched intervention and prevention, some of which were collaborated with U.S. scientists. Some achievements on etiological epidemiology have been obtained and the improvement of the 5-year survival rate by early diagnosis and treatment are the results of these achievements. It forms a fundamental basis for further research.

The second component studies the characteristics of cancer clinics in China. China has more than 200 specialized cancer hospitals and institutes. The equipment in the hospital and research laboratories has been greatly improved since 1949, which contributes to the

great progress in cancer diagnosis and treatment. In general, the successful integration of the whole-body regulation concept of Chinese traditional medicine into comprehensive therapy for cancer reflects significant progress in cancer treatment in China and contributes to the improvement of the five-year survival rate of several main cancers.

The third component studies basic cancer research in China and focuses on cancer hospitals and medical universities where most of the research is done. In contrast to other projects, cancer research usually gets more funds from the government every year.

The fourth component of China's cancer program is research on biotherapy before clinical trials. Recently, more mid-age and young researchers who have been trained abroad have returned and entered cancer research organizations. Quite a few of them acquired grants from the government. Many of them maintain their collaborations with foreign scientists and initiated their own researches. The gap in basic cancer research between China and developed countries is becoming smaller. The achievements in the cloning of new cancer associated genes and functional studies of them; the research on the mechanism and new ways of treatment on leukemia; the research on nasopharynx cancer and so on are the representative successes of recent years.

The fifth component addresses problems and prospects. Cancer remains the most ferocious enemy to the health of human beings all over the world, including China. In China, the increase of some kinds of tumors reflects the serious environmental pollution brought by industrialization. In many high incidence areas, the incidences of some cancers are still at a high level although many intervention and prevention measures have been adopted. Cancer prevention, including research on etiology, epidemiology, screening high-risk population, methods of early diagnosis, is far from perfect in this country.

For further research, great efforts are required to improve the quality of basic research and avoiding redundancy; enhancing co-operation between basic researchers and clinical doctors and among the researchers internationally; setting up better integration between traditional Chinese medicine and Western medicine. These efforts will lead to the development of new methods of treatment and enhancement of high incidence population studies in order to improve effective intervention and early diagnosis and early treatment.

Richard Mowery gave the next presentation on the organization and management of clinical research at NIH. In the U.S. NIH is a major sponsor of clinical research. The two major categories of applied clinical research supported by NIH are clinical trials and epidemiology studies. While each Institute and Center at the NIH is responsible for the management of the clinical research it funds, there is a general framework followed by each Institute and Center for organizing clinical trials and epidemiology studies.

For most epidemiology studies, funds are provided to perform the research at the discretion of the person who developed the hypothesis and designed the study. For epidemiology studies addressing high priority areas or are performed at multiple sites, the Institute or Center funding the research may take a more active role in the oversight and

management of the study. In some cases, an external Advisory Committee may be established jointly by the NIH and the investigator to provide on-going advice on the conduct of the study.

The general organizational structure for Phase III clinical trials supported by the NIH consists of: a national chairperson responsible for the overall conduct of the trial; a coordinating center responsible for data management, data quality and integrity, and statistical analyses; and clinical centers responsible for recruiting and following patients eligible to participate in the trial. Data and Safety Monitoring Boards (DSMB) are required for all Phase III clinical trials supported by the NIH. A DSMB is responsible for reviewing accumulated data for evidence of adverse or beneficial treatment effects during the trial and for recommending modification of the trial if necessary. The major responsibility of the DSMB is patient safety monitoring.

Belinda Seto continued the discussion of Data Safety and Monitoring Boards in her presentation on clinical trial oversight. NIH has had a long-standing policy, since 1979, of requiring data and safety monitoring for clinical trials. In 1998, the NIH updated this earlier policy by stating the guiding principles for monitoring (http://grants.nih.gov/grants/guide/notice-files/not98-084.html). Monitoring is commensurate with the level of risk, the size and complexity of the trial. For most phase III trials, a data and safety monitoring board is required. Furthermore, for multisite trials, it is important to establish an effective process for adverse event reporting and communication of the discussion and review of adverse events by the DSMB to the IRB (http://grants.nih.gov/grants/guide/notice-files/not99-107.html).

Recently the NIH has taken new steps to strengthen the oversight and monitoring of clinical trails. These actions include: (a) the requirement that applicants must submit a monitoring plan for phase I or II trials. The plan is subject to the review and approval of the funding Institute and Center, and awards are contingent on their approval (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html), and (b) principal investigators must report certain types of FDA communication to the NIH. These include warning notices and letters, consent agreement and clinical hold letters. Investigators must report to funding IC within 72 hours of receipt. Failure to comply may result in corrective and/or enforcement action.

There is also a new requirement for education — specifically, NIH requires key personnel who are responsible for the design or conduct of research involving human subjects to be educated on the protection of human subjects. To facilitate implementation, NIH made available a number of ready-to-use curricula, including the intramural computer-based program. Investigators have some flexibility to determine what is an appropriate level of education. Documentation of education is required before funds are awarded. NIH is currently developing a computer-based module designed for the extramural investigators that is expected to be available in January 2001.

Session V. Difference in Chinese and U.S. IPR and Bioethics Systems.

The five papers presented in this session formed the link between the previous sessions and the discussions to follow in the last session. These papers were:

- "Intellectual Property Rights (IPR) on Biotechnology in China: Current Situation, Problems and Counter Measures," by Dr. Xiu-Cheng Yu.
- "IPR Protection of Medicine in China," by Lincun Yang.
- "Technology Transfer at NIH," by Kai Chen.
- "Ethical Considerations in Conducting Cancer Epidemiological Studies in China," by You-Lin Qiao.
- "Bioethics: The Protection of Human Subjects," by Eric Meslin and James Lavery.

Dr. Yu pointed out that concurrent with the ongoing development of its reform and opening-up policy, China has made significant progress in IPR protection. The legal framework for IPR — including patents, trademarks, and copyright — has been developed. In the meantime, China has earnestly attended to its international obligations regarding the protection of IPR. Nevertheless, IPR protection in China is much lower due to economic constraints. As international competence grows, especially in leading edge fields of biology, we expect to learn more to offset our weakness, implement our policy, and adjust our strategy through wider international exchange and cooperation.

Dr. Yang asserted that China deems IPR protection as very important to the medical and pharmaceutical industry. As a developing country, China has achieved a lot in IPR system within the past decade, but Dr. YANG acknowledged that there is still a long way to go. China has built up a relatively good IPR system by promulgating many laws and regulations in field of IPR These include the Patent Act, Trademark Act, Copyright Act, and Trade Secret Act. In field of medicine, China has issued relatively good administrative laws and regulations. Up to present, China has signed almost all of the international treaties in field of IPR. China is strengthening IPR protections rapidly in enterprises and research institutes, and enterprises, universities and institutes have been becoming main bodies in IPR protection in China. But, IPR is still a tortuous phenomenon in China and a serious problem.

There are several IPR problems in field of medicine field involving administrative protections, the relationship between medical registration and patent protection, regulations relevant to clinical testing, and protection to genetic resources. In addition, there are new problems including problems concerning participation in the World Trade Organization (WTO), bio-safety of genetic manipulations, public order and moral aspects, and IPR issues in international cooperation.

Dr. Chen began with some background. In earlier days, before about 1980, the U.S. Federal Government was a major supporter of research both in federal laboratories and through grants to researchers. These efforts involved areas such as space and energy, but biomedical research at NIH was also a major budget item. In the decade of the 1980s there emerged a sequence of legislative events whereby the U.S. strengthened

identification of intellectual property and the protected access to it. The landmark legislation included the Bahy-Dole act of 1980, Stevenson-Wydler act of 1980, and the amendment of Stevenson-Wydler called the Federal Technology Transfer Act, 1986. This type of legislation evolved through the 1980s and into the 1990s with the present culmination in the National Technology Transfer and Advancement Act, 1995. This legislation spawned a new group of administrative structures in government agencies to facilitate management of licenses and agreements regarding IPR generated in Federal laboratories. At NIH, the focal point is the Office of Technology Transfer.

Dr. Chen then described the core licensing terms, license types, and provided examples of NIH issued patens and executed licenses. He pointed out that NIH cannot, as an agency of the Federal government, own a company. However, other institutions can. Research universities usually are associated with university foundation that can own companies.
The web site <www.nih.gov> is a good source of information on NIH licensing and technologies.

Dr. Qiao's presentation grew out of hi s collaborative research with Dr. Taylor as reported earlier in this forum. In recent years, the increasing biomedical research in China involving human participants has generated new ethical and logistical issues. Bioethics has expanded into all health professions involved in the sciences and practices of cancer epidemiology, prevention and control. Many professional groups have made ethical roles and guidelines. The profession of epidemiology is a recent example. Guidelines typically address conflicts of interest, scientific integrity; the risks and benefits of chemo-preventive agents to be used in randomized trials; genetic markers of cancer risk and notification, employment, and health insurance. The Chinese Guidelines on Ethical Review of Medical Research has been published by Ministry of Health in 1998.

Dr. Qiao pointed out that ethical theories commonly cited in biomedical ethics include utilitarian and deontological theories. Four principles of bioethics are beneficence, non-malfeasance, justice, and respect for autonomy of persons. There are no quantitative approaches to these principles, but judgment in a qualitative sense is called for.

The results in China are that the principles of respect for persons, beneficence and justice are recognized widely in China. Protecting the rights and welfare of human research subjects are responsibilities of Chinese researchers and their institutes. The large scale (N=29,584) randomized controlled nutrition intervention trial in Linxian farmers, was reported by Philip Taylor in the first session of this forum. Although the farmers who are enrolled in the trial may have an extraordinary risk of esophageal cancer, they were generally asymptomatic or free of disease at the baseline, and they may not develop esophageal cancer even in the absence of any preventive intervention. Thus, healthy individuals were randomly allocated to receive either multiple vitamin/mineral supplementation or placebo over 5 years. Both IRBs of NCI/CICAMS have proved the scientific research protocol and considered it had an acceptable balance between potential risks and benefits to the trial participants.

The continuing ethics reviews have been conducted by both IRBs annually for ongoing research activities. The information in the informed consent document is included description as research, constraints on experimental hazards, voluntarism in participating, scientific integrity, the safeguarding the privacy and confidentiality of research subjects and indication of placebo control. Concerning the ability of layperson (40% illiteracy) to adequately understand the potential risks and benefits associated with participation in the trial, a detailed group (community) informed consent was given by principal investigator instead of the individual will. However, individual consent was taken. Both signature and finger print will be acceptable for consent form. The adequate care and compensation to participants for illness during research have been provided.

Dr. Qiao concluded that IRB prior review on a research proposal in ethical terms is essential. Any research protocol should minimize potential risk and maximize benefits to research subjects. Individual or group voluntary informed consent from all subjects should be obtained. Protecting privacy and equal treatment of all subject are required. The adequate health care and compensation to participants for illness during research are strong recommended.

The next presentation, by Eric Meslin & James Lavery was presented in two parts — one by each of the authors. The title is Dr Lavery began by noting that Dr. Qiao's presentation was a very nice lead-in and complement to would he and Dr. Meslin would say. Dr. Lavery argued that the overall objective is protection — protection of human subjects of biomedical research. Toward the end of the presentation, Dr. Meslin observed that the use of the term "subject" has been the practice in the U.S. While "subject" has many interpretations in English, some of them are quite negative and can produce misunderstanding. Accordingly, he thinks it is desirable to discuss research involving human "participants."

The initial approach to the subject of issue of Protection of Human Participants of Research was the framework presented by Dr. Lavery — areas of the research process in which ethical issues arise. He provided the following list:

- Research question.
- Research design of trials.
- Recruitment of participants.
- Process of disclosure.
    - Informed consent.
    - Confidentiality, privacy, management of medical data.
- Regulation, oversight of studies.

This clearly is not an exhaustive list, but Dr. Lavery used is as a rough framework for his central point: each item involves the distinction between *process* and *substance* in ethics. — the procedural requirements of ethics are really what those processes try to achieve substantively in ethics.

He discussed each item and his remarks are covered in the paper. Here we use one — *recruitment of participants* to trials to illustrate the process-substance distinction. Most of you will be familiar with process distinctions liked signed consent versus proxy consent. On the substantive side, we know that there are all kinds of creative ways of implementing the process but the overarching issue here is respect for the person to assure a real willingness and voluntariness for people to allow things to be done to them that they might not ordinarily allow. Dr. Lavery pointed out that Dr. Qiao also presented this issue — respect for person — in his presentation. So, he argues, it is important always to go beyond process and procedures to a real substantive implementation of processes

Dr. Meslin then discussed the activities of the National Bioethics Advisory Commission (NBAC). The NBAC called a global summit of national bioethics commissions to promote dialogue about ethical issues that arise in research. This global summit has met on two occasions in Tokyo and in London. There are national commissions in 38 countries so far that have met to discuss those bioethics subjects that they feel they have in common. At the same time, there are a number of U.S. initiatives in this field. There are initiatives by NIH that you have heard about. There are also initiatives by our Centers for Disease Control and Prevention, the Institute of Medicine, the American Association for the Advancement of Science, and the National Science Foundation.

Dr. Meslin said that the message he wanted to present to the participants of the Forum is that beyond all of the U.S. regulations for protection of human subjects there is the realization not achieved complete harmonization. The U.S. has a complicated but, it is believed, reasonable and understandable set of regulations for its own investigators. Many are now observing that it is time to consider other countries and to strive to harmonize among them. The NBAC is among the efforts addressing this. But one of the opportunities for harmonization and collaboration is to recognize that there is no single set of international or national guidelines that has been agreed upon by every nation in the world, by every investigator in the world. While this might seem to be a very unfortunate situation, Dr. Meslin took an optimistic view that China, the United States, and all other countries have the opportunity to look carefully at how research is conducted collaboratively between and among our countries, and to find areas where there are difficulties that need to be worked through.

Dr. Mesling hoped that his last slide — *Some Possible Next Steps* — would be an introduction to the small group discussion on bioethics to follow in this forum. This area of international regulation and oversight of research is very fertile ground for discussion and cooperation for several reasons. First, there are many international guidelines and regulations, none of which have moral authority over the whole world. Second, it is important to recognize that through most advanced communications — e-mail, Internet, CNN, and news media — we are learning more quickly about research that is occurring in other countries and we are learning about the difficulties and problems that arise.

PART TWO: CHALLENGES FOR SCIENTIFIC COOPERATION

Session VI. Discussion of Issues and Differences.

There were two Small Group Discussions reporting in the Plenary Session.

- Biodiversity and IPR. Keping Ma and Joshua Rosenthal, Co-Chairs.
- Bioethics and Clinical Research. Jisheng Han and Eric Meslin, Co-Chairs.
- Plenary: Options for Policy and Procedural Changes to Facilitate Research Cooperation.

Dr. Rosenthal presented the report on the discussion of Biodiversity and Intellectual Property Rights. For the purpose of this meeting "Biodiversity" includes human genetic diversity, although it is generally separated in policy discussions. He then presented the following issues identified in the group discussion as policy challenges to collaborative research:

1. *Differences between U.S. and China policies on what constitutes a patentable invention*. Specifically, the patenting of DNA sequences with minimal understanding of their genetic function is not allowed in China. U.S. scientists also frequently see this as a barrier to research, and collaborative research.

2. *Costs of patent prosecution and maintenance are prohibitively high*, particularly in the U.S., for developing country scientists and their organizations.

3. *Lack of legal clarity and/or consensus among scientists regarding shared rights in a collaborative research project.* Such rights may include design of research question, direction of a study, authorship, as well as ownership and/or compensation related to a commercialized invention. In particular, the role of the sample provider, their community, or institution is unclear.

4. *Access to biological materials is complicated by unclear and developing regulations* restricting their transfer and the absence of clear standards for informed consent and for compensation.

5. While the principle of *special rights of indigenous peoples to biodiversity* is widely recognized, in practice it is difficult to define the individuals, communities, organizations or tribes to whom these rights accrue.

6. The increasing probability of commercialized outcomes from a research project may already be inhibiting basic science in some cases. Proprietary interests in research products are in some cases slowing access to samples, sharing of data, and publication of results.

Some guidelines for cooperation that were suggested by the Chinese delegation and widely supported: (See paper by Chinese Delegate from the Health Ministry)

1. Equity and voluntarity in design of project
2. Mutual benefit
3. Mutual participation
4. Equitable sharing of benefits
5. Mutual ownership of patents

In the discussion following this report, Eric Meslin highlighted the group's proposal for a bilateral-bionational agreement. Dr. Meslin mentioned the Global Fund of the National Bioethics Advisory Commission with those countries that have established national bioethics advisory groups in one form or another. It is a group that created itself under no authority or auspices of any international organization. This past September it met again and at that time my understanding that the ethics committee of the Chinese Ministry of Health has not been identified as a national commission per se. But we have had very instructive participation by Dr. Qiao from China. There have been other Chinese involved, including lawyers, who have been involved in Global Summit activities. Dr. Meslin believed that the proposal for bilateral-binational arrangement would be very welcome by this group.

He added the forum group should know that the US National Bioethics Advisory Commission exists by Executive Order signed by President Clinton. The commission expires October 2001 unless it is reestablished by the next president whoever he many be. Meanwhile, there have been a number of bilateral meetings between many bioethics commissions. I think it is a very worthwhile project and the bioethics community has strongly endorsed those kinds of commissions.

Dr. Meslin thought his group agreed with the view expressed Joshua Rosenthal for the other group that the formation of commissions and activities around intellectual property rights goes far beyond the responsibilities of this particular forum. However, he said it is important to signal from the perspective of the scientific community our concerns and interests in the issues of intellectual property from both the perspective of the protection of intellectual activity and stimulation of international research. But also our concerns and interests about the ultimate accessibility of the product of that research to the population in need of new medicine, new medical technology and all the fruits of biomedical research. We should not be excluded from the discussion that occur. In the U.S. other parts of our government structure agreements with the legal and commercial aspects of intellectual property. But I think the record of this meeting will reflect the concern and interest of the scientific community.

That closed the Plenary Discussion on the report of the Biodiversity and IPR group. Dr. Keusch called on Professor Han to provide a summary of the discussion by the Bioethics and Clinical Research Group.

Policy challenges were identified by the Bioethics and Clinical Research Group, but the group did not make recommendations as bold at the previous group. The following seven items were identified.

1. We identified recruitment a bioethical policy challenges, especially in three areas: HIV-AIDS, cancer, and drug abuse. The recruitment problems arise in these areas because scientific knowledge is desperately needed in all three and the scientific knowledge itself creates an expectation on the part of the public that the underlying problems will be addressed. Yet, while there is a public interest in resolving the problems, the issues raise what we call "socially sensitive" questions. And when one is doing research in areas like HIV-AIDS or drug abuse, the research questions and research methods are themselves socially sensitive. We found that in China, as well as in the U.S. it is often difficult to overcome some of the public perceptions that the science might want to answer.

2. The second topic arose from the discussion that followed the work of Drs. Taylor and Qiao regarding disclosure of information in public health. These raise the familiar topic of how one distinguishes between those issues felt to be important for disclosing to an individual about their own risk-taking behaviors and the information that is needed in order to protect them from the reactions of the community.

3. From the Chinese perspective, when one considers what is termed "transfer of non-western treatment" to the US, how does one consider the return on scientific knowledge? Acupuncture, as discussed by Dr. Han, is a good example. The very nature of the intervention many not lend itself to engagement in discussion.

4. This issue has two components — medical records and privacy — motivated very much by the genetic studies referred to yesterday where issues such as potential misuse of information, the need to monitor and train investigators and review committee members, and to inform the public. All need to be taken into account in which the research is being done. I should note that the group is trying to make it clear that these were not only policy challenges facing China, but in the US as well. We wanted to make clear that in collaborative research, these challenges are trans-national or bi-national and must be addressed by both sides. A good example is the apparent inconsistency in the US among various state laws, or even the absence of state law in some cases.

5. This issue has been extensively discussed in the international literature, namely what to do when a study provides useful information and potentially even a useful product. Is there any responsibility to provide the "study benefit" to individuals, communities, or countries? Most of the suggestions on how to deal with this issue focused on the instrument of prior agreement. It was argued that the instrument itself might be less important than the philosophy or principle behind it. The implication is that one should begin thinking about out-trial benefits as early as possible. Historically, research has not considered likely benefits. When

it has, it has not been considered as part of the research protocol and certainly not part of the ethics review. Our group was mindful of the scenario where successful collaboration potentially with a large study could produce benefits. We have heard of many examples in both low-tech and high-tech models where the policy challenge was the no one had anticipated what to do afterward. Yet, there are many very good reasons for going forward with a policy of making treatment available. That does not solve the problem entirely because various clinical trials may be testing different levels of care. This begs the question of whether standards of care in two countries need to be factored into this particular policy challenge.

6. As a policy matter one ought to focus on the low-technology alternative. Is it realistic to study and test a very expensive drug or intervention that has no change of becoming available in China? We have, for example, already heard that triple therapy for AIDS is not an option, as it cannot be paid for. It became clear that economic issues are themselves policy challenges. How do you factor in the cost to developing countries of actual or potential programs?

7. Finally, an issue that we put on our agenda in this morning's session and wanted to be sure was brought up here is the various mechanisms for oversight. We discussed and were pleased to be informed from the U.S. side that the IPR and ethics review group had stated the same kind of issue. Namely, whether a local committee in a small community has as much expertise as a larger national committee that can review multi-center studies. The subject of the Data Safety and Monitoring Board (DSMB) was raised by some of members of the US delegation and we found that these groups do exist in China but not in the same form. It is clear that these various mechanisms for oversight could present a policy challenge if US sponsors required them while Chinese sponsors did not. The last part, that I think is ubiquitous, is the levels of expertise necessary in oversight of international or bi-national research including the ethics committees themselves, the investigators, and the research participants.

Dr. Keusch provided summary observations:

One of the things to be stressed is that the issues brought up do not have an immediate or clear resolution. We cannot say "here are the rules and regulations, please use them." This is a process of evolution and we are learning by finding new examples that challenge our concept of what is ethical and what is feasible. That suggests that in the area of collaboration between the U.S. and China, the establishment of an ongoing dialogue is going to be extremely important. We must work constructively to identify problems in order to understand the issues that will lead to identification of solutions to allow us to move forward.

Many of the issues that were brought up today focused on clinical trials, but there is hope that other research briefly touched upon (for example, ethnological studies, social science, and behavioral research) have there own unique issues and ethical concepts. Are

there any additional comments or thoughts along those lines? It is very artificial to separate biodiversity, intellectual property rights, clinical research, and bioethics as they really interact with one another. I think we need to keep that in mind in the future. Now I think we can move to closing comments.

Closing Comments.

Dr. Zu: I am delighted to be here delivering the concluding remarks. Please allow me, on behalf of the NSFC, to congratulate on the total success of the Joint Policy Forum. And I would like to thank our US host for their gracious hospitality.

As is agreed, biotechnology and biomedicine are among the world's hottest research topics. Beside scientific approaches, issues like intellectual property protection, ethical undertaking, barrier-removing efforts and international cooperation play an important role as necessary guarantees in the smooth deployment and development of the research. To identify these issues, and to find out a way in which these issues are fairly addressed to facilitate the research instead of hampering it, is just what this Forum aims at. We are pleased to see that through the one and a half day of keynotes speeches and extensive discussions, we have effectively deepened the understanding in policy issues related to biotechnology and biomedicine in the two countries, established or expanded personal contacts for collaboration, and had comprehensively thoughts on the next step forward. We believe that this forum has not only opened channels for all related sectors to exchange views and learn from each other, but also offered valuable consultation for both NSFC and NSF in our effort to optimize our funding and research portfolios, as well as to provide substantial guidance and coordination in the adjustment of working strategies.

As a national science-funding agency, the NSFC shoulders an important responsibility in improving research capacity of the nation and organizing top-down research programs in all areas of basic science. For that end, the NSFC is proposing the following steps and means for collaboration with NSF, NIH and other relevant organizations:

The decade-long series of dialogues on policies between NSFC and NSF, which has seen the first two successful forums with different themes, has been proved to be timely and effective in bridging sectors concerned, promoting the understanding of policy-related issues among these sectors and by the general public, and initiating substantial collaborations. In the years ahead, we should continue our efforts in recognizing the mostly interested topics with implication to scientific, engineering, social and economic development, further strengthen the understanding between policy researchers in the two countries, and enhance both on policy level and on research level;

Based on the common interest in building resource and developing manpower, the NSFC is willing to get involved or co-sponsor training programs with US research institutions, funding agencies as well as research universities, in areas related to biotechnology and biomedicine:

- To bridge sectors and individuals working in similar or relevant areas, we support the idea of holding international workshops or seminars by co-sponsoring them or encouraging the participation of Chinese scientists who are grantees of the National Natural Science Fund. We will be delighted to work with NSF, NIH or other funding or research organizations in this aspect. Priority areas or critical issues like IPR, cancer research, infectious diseases, bioethics in clinical research are among our considerations;

- For projects with common interest in life sciences, we propose to jointly initiate and fund collaborations with NSF, NIH and other relevant organizations;

- Chinese life science community would like to take more active part in major or cutting-edge research programs with their international partners, and NSFC shall promote the participation by Chinese scientists in our capacity. We are looking forward to the responses from our US counterparts;

- IPR, with an emphasis on biotechnology patent protection, is an area in which both China and USA have mutual interest and concern. We propose that related sectors in our two countries keep strengthening understanding of each other, and explore the possibilities of making joint efforts;

- In the area of bioethics, I couldn't agree more with the opinion that harmonization of concept, systems, standards and procedures of ethics among all nations doesn't necessarily mean that they need to be exactly the same. The important thing is that we should find out what is going on in another country, share the information and make joint research. A cooperation research, together with adequate joint funding, is highly expected;

- This Forum has also identified several barriers, ethical dilemmas and policy challenges to the effective and efficient research. Although some of these issues are beyond the responsibilities of the Forum, I think it is important for us to understand them, think about the improvement, and act properly. I also hope that our discussion in this Forum would raise the attention from government agencies, funding organizations or professional groups for a joint solution.

It is our sincere wish that this forum would be a good start of cooperation in policy issues in biotechnology and biomedicine. We also wish that it had drawn the attention of all relevant sectors and of the general public.

Dr. Keusch: Thank you. As part of this theme of harmony I would like to acknowledge the role played by several individuals in allowing this meeting to be. I give great thanks to our translators who have done a superb job. Thanks to Judy Levin has been so much involved in the logistics to make sure that everything worked well. Thanks to our staff at Chiles International House, Michelle, James, and colleagues who provided the meal services and refreshments and cleaning up to make sure everything is in order, and to all the people who have been involved in the logistics of the meeting. Thanks, certainly, to all the participants on both sides for giving your time, energy, and influence. In the theme of harmony, we are at the end of the meeting, but really at the beginning of something. We have not completed the job; we have begun the job.

I would like to comment on the decade-long program of science and technology forums that the NSF of the United States and the NSFC of China have embarked on. From the policy perspective of the NIH, we are pleased at being included in the policy forums from the beginning. It is our great pleasure to work with Alex DeAngelis, Rita Colwell, and all the policy staff at NSF. The interactions between the National Science Foundation and the National Institutes of Health are already vigorous and strong. But they are in fact growing stronger and more vigorous in many other areas.

We have identified significant issues that we need to address. Issues about bioethics and intellectual property rights are the ones in evolution. We will find that there are differences in our views of how principles are to be put into practice. But we must return to the basic issues, the fundamentals, the principles, and understand what the differences in practice and process really mean. Some of us will discover through collaborations that bring up new issues, issues that we will have to return to the table to solve. We have already held a number of meetings over the last year-and-a-half with various colleagues in China — bilateral meetings between NIH and colleagues in China.

I am sure that NSF has done the same thing outside of the boundaries of this forum, but Alex DeAngelis will address how we are going to integrate all of these various activities. Alex is not only involved in the organization of this meeting in a major way, but also in the organization of the delegation of leaders from NIH to China several months ago to talk about the process by which we support and review research — the peer review process, funding mechanisms, and all of those issues that will allow collaborative research to take place. As I mentioned earlier to other institute directors who have been or are interested in visiting China because of the opportunity for bilateral collaborative research, conducted in ethical fashion, that meet mutual priorities and benefit. But it goes beyond bilateral US and China activities as we are part of a global international biomedical research network and we participate in that network as individual countries. As Eric Meslin mentioned, Chinese participation in global forum in bioethics and in other similar forums give us an opportunity to continue the discussion. At the NIH we are very interested in continuing to look at opportunities for clinical research, for research in the areas of genetics and biodiversity, and in other areas. I think the sessions of the last day-and-a-half will help us facilitate the interactions that can develop from our continuing dialogue. So I would like to call on Alex DeAngelis to say a word from the perspective of the NSF, the organizing entity for the overall program of these science policy forums.

Alex DeAngelis: I don't really have much to add to what Dr. Keusch has said — just a few points. This forum was the second in a series we hope to continue, a series of dialogues on policy issues related to science and technology that we hope to continue over a ten-year period. We started in Beijing in October 1999 with a very large meeting on issues of science and technology in the knowledge-based society. We proceeded with this meeting and we are planning the next meeting right now. a meeting to deal with the various aspects of engineering education. That meeting will probably take place in October 2001. The subjects discussed at this meeting — biomedicine and biotechnology — are quite broad so there is more to explore. There will be many occasions in the future for considering what we should do next in this powerful dialogue area. Not only is it in our framework but more broadly in United States and China relations.

I wish to thank all of you, Chinese and American participants, for helping us to identify the issues with which we should be concerned now and in the future. Dr. Zhu identified some of these in his remarks. I recall Dr. Zhu mentioning the issues of bioethics in cancer research, infectious diseases, IPR, and others. Thus, there are many possible areas for us to work with in the future. NSF and NIH will be sharing information as a matter of common practice. We will continue the dialogue on a regular basis and we will openly share our information with our colleagues from the National Science Foundation. So while I cannot say at this moment what the next step will be in the biomedical and biotechnology area, your wise council will help us decide what they should be. Perhaps some of you may be called upon again to be involved and contribute.

Before we held this meeting, I received quite a few calls from people who are not here. Those people represented research in drug companies. We said no, for this meeting. But outside Washington and the government, as you well know, there are a great many people who are interested in the kind of dialogue that we have had here. Not the least of all these are drug companies. They were not much mentioned here, but they are very much involved with the problems and issues — and their solutions. Perhaps at some point in the future we can actually bring them into the dialogue.

The two discussion groups that reported this afternoon touched on at least one common area. There may be more, but the one I heard was from the biodiversity and IPR group. That group observed that there is a danger of viewing all research as potentially commercial. Then, the bioethics group mentioned the need to and questioned whether prior agreements that include consideration of post-study benefits. All of this relates to how the value of research and collaboration is determined in a commercial sense. As someone who has been involved in US-China scientific exchanges for about 30 years, I want to quote a famous Chinese politician, "It is glorious to be rich." I think, at the same time it is also glorious to pursue the development of knowledge together. I hope we can maintain that kind of attitude. I know scientists who want to maintain the freedom to pursue common knowledge. From NSF's point of view and I think also from NIH's point of view, the pursuit of knowledge together is glorious. We should work toward doing that.

Finally, from my worm's-eye view of the world, having dealt with US-China relations since 1973, I want to point out something obvious, so obvious that it may go unnoticed. What we have done here in the last two days compared to where we were thirty years ago is truly amazing. Think back to what it was like thirty years ago when we first had contact. You will recall how nervous each side was, the political problems, the language problems, the communication problems, and all the other problems I don't need to mention. We have come a long way since that time. I congratulate everybody here for working so hard for the cause of scientific collaboration so as to be able to reach this stage where we can truly meet as friends and discuss things frankly and openly without being afraid of hurting each other's feelings. Among friends, there is no such thing. Thank you very much.

III. FORUM PAPERS

Rita R. Colwell: Keynote Address

Current and future colleagues, it is my pleasure to welcome you to the Second U.S.-China Science Policy Dialogue. I especially want to extend greetings to my good friend and colleague, Prof. Zhu Zuoyan and to Delegation Co-Chair Professor Han Jisheng.

I feel it is appropriate to recall a quote from the introduction to the proceedings of the first U.S.-China Science Policy Dialogue. It comes from Confucius. I won't attempt the Chinese pronunciation, but the English translation truly fits the occasion: "Is it not a joy when friends come from afar?" We welcome your participation in cooperative research with American scientists.

This is the second in a decade-long series of U.S. - China science policy dialogues. This meeting is sponsored by the U.S. National Institutes of Health, the U.S. National Science Foundation, and the National Natural Science Foundation of China. We hope there will be many opportunities for joint research with our Chinese colleagues. I would like to open our gathering by speaking briefly about a field that I have been deeply involved in developing—marine biotechnology—and research opportunities within the field. Then I will say a few words about cooperative research - both in terms of the challenges we face and some of the most valuable opportunities.

Seventy percent of the Earth is covered by oceans. They touch every continent and most nations. We think of the oceans as a constant, yet they are ever changing. This is a result of geological movements in the ocean floor and natural ecological changes (such as currents and temperature). The oceans are now changing as a result of our species' intervention. This comes in the form of pollution, oceanic dumping of wastes, and over fishing. We take the oceans for granted. Modern fishing methods have decimated once fertile fishing grounds such as the Grand Banks off the coast of Newfoundland, which was closed for cod fishing. This nearly destroyed the fishery industry in coastal New England. And as fish become scarcer in the upper reaches of the ocean, fishing trawlers extend deeper into the waters looking for fish. A major concern is that they destroy fragile coral ecosystems as they scrape the ocean floor.

This is a potential tragedy for our planet. Despite our new abilities to study the ocean's depths, we still know very little about the oceans. In each drop of ocean water, for example, nine out of every 10 microorganisms are completely new to us. In November 1997, I had the pleasure of participating in the Marine Pharmacology and Cultural Technology of Seaweeds Training Course held in Qingdao. At that meeting, Prof. Guan Meijun of the Drugs Institute of Qingdao noted, "The 21st century will be a marine economic century." I cannot agree more. This potential marine economy will present us with numerous opportunities for scientific research and development.

We define marine biotechnology as "the application of scientific and engineering principles to the processing of materials by marine biological agents to provide goods and

services." The field is broad and encompasses numerous subspecialties. Humans have always relied on products from the sea. Today, products resulting from marine biotechnology are of great economic value. The potential development of products from marine sources is tremendous and yet unrealized.

Among the success stories of marine biotechnology are the marine toxins tetrodotoxin and saxitoxin. Both are used as research molecules in neurophysiology studies. Tetrodotoxin is an extract of the pufferfish, called "fugu" in Japanese. It has been identified from other species of fish, marine invertebrates, algae, and some amphibians. Saxitoxin is isolated from dinoflagellates. Both are among the most potent neurotoxins known. They block voltage-gated sodium channels in neurons. Seminal studies on neurophysiology and neuropharmacology using these toxins were first published in 1960. These two marine toxins have been essential — and remain essential — for our understanding of the role of sodium channels and the physiology of the action potential in nerves.

Green fluorescent protein (GFP) is an extract of certain species of jellyfish and other coelenterates. It, too, was first discovered in the early 1960s. It now is used as a marker for gene expression, protein localization, and localization of calcium within the cell. In this slide, GFP is linked to the simian immunodeficiency virus (SIV) and is used to track the movement of the virus through the macaque's immune system. The green fluorescence can be seen in CD3+ T lymphocytes, indicating the presence of the virus in these cells.

With the discovery of extremophilic microorganisms from heat vents in the ocean's floor — and the later discovery of extremophiles that tolerate extreme cold, high salinity, high pressure, and other environmental extremes — scientists have unveiled new sources of microbial enzymes. Modern genetics research now depends upon many of these enzymes for gene splicing, cloning, and genomic analysis. Our increasing knowledge of marine organisms is allowing us to maintain and grow some commercially valuable species in aquaculture — sometimes in polyculture in which several different species are maintained together.

Society stands to benefit from marine biotechnology research. The benefit will not only be the increase in knowledge of the marine environment; it also will be in the discovery and development of new food, drug, and industrial products. My own research with Vibrio cholerae illustrates the broad reach of the field of marine biotechnology. Robert Koch identified the organism we now know as Vibrio cholerae as the causative organism of cholera. The disease originated in the Ganges delta on the Indian subcontinent, and traveled across large portions of the world in a series of pandemics beginning in 1817.

By the mid-1800s, British physician John Snow realized that cholera was spread through drinking water contaminated with sewage. But it wasn't until 1959, more than 100 years later, that Sambhunath De discovered the Vibrio toxin. This toxin changes the permeability of the cell membrane in the intestine of infected individuals.

In the 1970s, my colleagues and I realized that the ocean itself is a reservoir for Vibrio. We identified V. cholerae in water samples from the Chesapeake Bay off the coast of Maryland and Delaware. We later used immunofluorescent techniques and identified these organisms. The organisms are difficult to culture, and they live within copepods, the zooplankton that harbor the dormant Vibrio. We have used the latest genetic techniques — PCR and gene probes--to detect Vibrio directly from environmental samples.

Our most recent studies have used remote sensing imagery and sea temperature and height data to determine the periodicity of cholera outbreaks in Bangladesh. We have found a positive correlation between increased sea surface temperature, and an outbreak of cholera that follows several months later. We recently published a brief communication in Nature on the likelihood of transport of pathogens via ship ballast tanks. This was based on our measurements of Vibrio cholerae in ballast water.

Such introductions not only can have a negative effect on human health, but they can also have major effects on aquatic ecosystems. We have learned this lesson from of the introduction of zebra mussels into the St. Lawrence River and Great Lakes through ships' ballast water. This research with Vibrio cholerae highlights a larger scientific challenge: what appears to be a small biological problem — an organism that infects people — can have ramifications and interrelationships that are of great magnitude. Thus, our work has touched upon biodiversity, biocomplexity — which I will define in a few minutes — and even genomics, as we shared in the sequencing of Vibrio cholerae genome. Moreover, this is truly a product of international cooperation, the kind of cooperation we wish to foster between researchers in the U.S. and China.

Let me now discuss some of the ground rules for foreign research institutions that wish to do research under the aegis of NSF. First, foreign institutions cannot apply directly for NSF grant money. They must have a U.S.-based partner. I should also note that NSF does not fund biomedical research related to clinical medicine and testing. That is funded by NIH and will be discussed later in the program.

The structure of NSF includes Directorates and there are Divisions under the Directorates. For example, the Division of Environmental Biology and Division of Integrative Biology and Neuroscience are under the Directorate for Biological Sciences. Within each Division there are programs. Grant applications are submitted at the program level. Some special programs cut across divisional lines. For example, biocomplexity awards go to large, multidisciplinary research projects that study interrelationships from the molecular to the ecosystem levels. Similarly, the Arabidopsis genome project — to determine the function of all 25,000 genes of Arabidopsis thaliana within the next 10 years — involves five divisions within the Biological Sciences Directorate.

NSF provides funds for other activities as well. We also support conferences in areas of scientific importance. Other important mechanisms are what we call incubatory grants. These are enabling grants that allow researchers to hold a meeting or workshop that allows potential participants to learn of a proposed project. These grants allow

researchers— perhaps from a number of institutions - to determine their roles in a potential grant application prior to its submission.

I'm going to pull just a few examples from thousands of studies NSF has recently funded to give you an idea of the breadth of the work we support. We currently fund a number of projects involving researchers from China. The NSF's relationship with China extends back nearly 20 years, to the signing of our cooperative agreement that sent American scientists, social scientists, and educators to do joint research in China with their Chinese colleagues. These early ties have resulted in long-term relationships between Chinese and American scientists.

NSF recently funded a project led by Erle Ellis at University of Maryland Baltimore County to study long-term changes in the biogeochemistry of carbon, nitrogen, and phosphorus in agricultural villages in China. In this photo, scientists in Jiangxu Province are replicating a traditional use of waterlogged compost — anaerobic production of compost in a pit. This method is specific to this region of China. The NSF funds biodiversity studies at all levels, from microbes to ecosystems. One of our long-standing projects has been providing funds to develop Science and Technology Centers, centers of excellence in cross-cutting areas. For example, Michigan State University is home to the Center for Microbial Ecology, an 11-year-old project. The goal of the center is to support work to understand factors that influence competitiveness, diversity, and function of microorganisms in natural and managed habitats.

One of their most recent initiatives, which was demonstrated to me not long ago, is a computerized image classification system. This system, based on software the Center has developed, allows researchers to rapidly and accurately classify microorganisms by morphotype. This may lead to new technologies for real-time monitoring of bioreactors to ensure their optimal performance. This classification system is an example of multidisciplinary work among computer scientists, microbiologists, and engineers to advance understanding of the complexity of natural communities. The Center has international collaborations with Japan, Russia, and Germany, and invites such collaborations.

Genomics Is an important thrust of NSF grants. One of our recent successes has been the publication of the genomic sequence of the extreme halophile, Halobacterium species NRC-1 in the Proceedings of the National Academy of Sciences. The work was carried out by a multiuniversity team led by Leroy Hood of the Institute for Systems Biology in Seattle and Shiladitya DasSarma of the University of Massachusetts, Amherst.

NSF is funding new ways of using information technologies, while at the same time supporting more traditional research into animal and plant systematics. Last year, we funded work on the basic systematics research on clams of the family Veneridae. This includes state-of-the-art computer supported 3D analyses of anatomical characters along with DNA studies. It also included the development of a taxonomic database for the family. The work is being carried out by scientists from the Field Museum of Natural History in Chicago and the American Museum of Natural History in New York. One of

the goals of the project is to establish an international bivalve phylogeny working group to allow for international interactions and joint research.

Our biocomplexity grants are among our newest multidisciplinary collaborative projects. The NSF is devoting an increasing amount of our budget to these systemic studies and we plan to host a workshop on biocomplexity projects in 2001. NSF just funded a number of projects in October:

- One is a study by researchers from Cornell University of water movement and ecosystems in watersheds connected to Lake Ontario.

- Another involves the use of mathematical models and empirical measurements to study principles related to life history. It is led by a consortium led by scientists at the University of New Mexico, and it is studying the abundance, distribution, and species richness of organisms in scale with body size, space, and time.

These are just two examples from a varied and growing portfolio.

The NSF also supports the development of special courses. We now are working on ways to make these courses available to our foreign colleagues. An example of the kinds of courses we support is a six-and-a-half week summer course in molecular approaches to microbial diversity given at the Marine Biological Laboratory at Woods Hole. The first course, developed by Caroline Harwood of University of Iowa, was given this summer and will be repeated for the next three summers.

The NSF also funds work on drug discovery, biodiversity conservation, and sustainable development through the Fogarty International Center here at NIH. This program screens biotic resources with the intention of discovering pharmaceuticals from natural products.

This tiny sampling of NSF's bioscience-related programs should give you an idea of the kinds of studies we support. Alex and Bill can help you find additional information, and you are always welcome to explore our web site at www.nsf.gov.

Now that you have an idea of what we support, the next question is where do we go from here? This is the second in a series of three meetings in which we hope to discuss ways in which Chinese researchers and educators can interface with their American counterparts. Such interactions are not always simple. Our meetings should create methods and protocols to identify and hopefully overcome any obstacles.

Among the obstacles are questions of intellectual property rights. I believe our goal as scientists should be to communicate with each other about the benefits of collaboration, while also addressing any outstanding questions on this issue. We hope these meetings will foster a productive exchange of ideas. We may come from different national systems, but we share a similar and rigorous scientific heritage and culture.

Research on biodiversity is an especially vital area. We must have plans in place to protect species that are rare or endangered from overexploitation or habitat loss. But we cannot know what plans to make unless we have completed biodiversity and biocomplexity studies in various ecosystems. Our meetings will aid in developing plans for such studies.

I know that some of the NSF funded research I've mentioned today probably has whetted your appetites for participation in a large, multinational study. Unfortunately, we can't just tell you to go out, find a U.S. institution as a partner, and come back to the NSF for funding. This meeting and those that follow will set the groundwork so that we will have the structure in place to assist you and your colleagues in China to locate these potential partners.

In closing, let me just say once again that we enjoy many possible avenues for cooperation. The world is truly getting smaller. Twenty years ago, when NSF and China began our scientific exchange, communication was by letter, telegram, and, if both sides were lucky, by telephone. We all know that things have changed. At a recent scientific meeting, an U.S. scientist explained how he simultaneously ran research laboratories in China and here in the U.S. The wonders of high-speed communication via the Internet allow his U.S.-based team to receive data collected in China once a week. He explained that, in fact, he could receive data daily if he so desired.

With rapid communication and personal meetings such as these, we can begin to establish arrangements for joint research. We therefore hope and expect to see numerous U.S.-Chinese teams of scientists working on multidisciplinary research projects in the years ahead. Once again -- thank you for joining us, and welcome.

Session I: Areas that Offer Mutual Advantages for Cooperation

YE Xinsheng: An overview of funding to the biomedical research in China via the Department of Life Sciences, NSFC

National Natural Science Foundation of China (NSFC), one of the government agencies under the direct jurisdiction of the State Council, was established in February of 1986. The main responsibility of NSFC comprises making an effective use of the science funds, directing, coordinating and financing basic research and part of applied research, identifying and training talented persons and promoting the advancement of science and technology and the economic and social development.

NSFC is composed of 7 academic departments, 4 bureaus and 1 administrative office. The department of life sciences, the largest department, is subdivided into 3 sectors: the biology sector, the basic medicine sector and basic agriculture sector. The Biology Sector includes 7 discipline Divisions which are: Division of Microbiology and Botany, Division of Zoology and Ecology, Division of Biochemistry and Molecular Biology, Biophysics and Biomedical Engineering, Division of Neuroscience and Psychology, Division of Physiology and Pathology; Division of Cell Biology, Developmental Biology and Genetics.

The Basic Medicine Sector includes 4 discipline Divisions which are: Division of Preventive Medicine and Immunology, Division of Basic Research in Clinic Medicine, Division of Materia Medica and Pharmacology, Division of Traditional Chinese Medicine and Materia Medica. The Basic Agriculture Sector includes 2 discipline Divisions which are: Division of Basic Research in Agronomy, Division of Basic Research in Veterinary Medicine, Animal Husbandry, Forest Sciences and Aquatic Sciences.

Government allocated funds is the main financial source of NSFC. Its annual budget has been rapidly increasing, from 80 million Yuan RMB in 1986 to 13 billion Yuan RMB in 2000. According to the size of the grants, currently there are mainly 3 award categories in NSFC: general projects, key projects and major projects. General projects mainly include investigator initiated projects, projects for young scientists and projects for developing regions.

About 60% of the budget goes to support general projects; the average award amount of general project has increased to 180,000 Yuan RMB per project. Key and major projects account for 20% of the total annual budget.

During 1996-1999, the Department of Life Sciences has funded 16027 general projects with a total budget of about 10 billion Yuan RMB; 153 key projects with a total budget of 127.8 million Yuan RMB; and 15 major projects with a total budget of 78 million Yuan RMB. Among these projects, the areas of research emphasis include immunology, tumorology, neuroscience, traditional Chinese medicine, post-genomics, and infectious diseases.

With the completion of human genome sequencing, biomedical sciences is standing on the threshold of research advances that were once inconceivable, its research emphasis is turning to the whole of human health as well as the research on diseases.

In the future, the Department of Life Sciences will place an even higher value on biomedical research, and will give special encouragement to the projects employing novel concepts, approaches or methodology; projects making use of advantages and resources of China and projects integrating the biomedical research with research in other disciplines such as mathematics, physics, and material sciences

Session I: (continued)

QIN Bo-Yi: Present Situation of New Drug Research in China

New drug research in China has a long history. We have excellent professional ranks, integrated branches of learning, rich resources and favorable time for research of new drugs. So in the latest half-century, more than 50 kinds of inventive drugs have been approved for marketing in China. Among them, drugs exerting influence in world are anti-malarial drugs artemisinin, benflumentol, and a series of their derivatives, sulfhydryl detoxicating agents, such as sodium dimercaptosuccinate, and cholinesterase inhibitors such as huperzine A.

In recent years, treatment of leukemia with arsenides has succeeded. Over the last fifteen years, rapid progress also has been made in production of drugs by biological methods. Development of genetic recombinant human growth hormone has succeeded and over eleven kinds of drugs produced by genetic engineering have been approved for marketing. Eight preparations have been included in the pharmacopoeia of the People's Republic of China. Still another fourteen kinds are in the clinical trial stage.

In China, most achievements in medical scientific research can be relatively quickly applied to medical health care work. For instance, the infectious diseases have changed from the first position in causes of death in the 1950s to tenth position now. The mortality of cardiovascular diseases has decreased from 40 percent in the 1970s to around 10 percent at present and the five-year cure rate of cancers has attained 39.1 percent. The endemic diseases that were seriously harmful in the past, such as schistosomiasis, kala-azar, filariasis, endemic goiter and Ke-shan disease have been controlled. The comprehensive effect of these achievements was reflected in the prolongation of average life span from 35 years of age for the 1950s to longer than 70 years today. On the basis of these achievements, we shall take better measures for and put more human and financial resources into research on new drugs in the future.

First of all, we shall be confronting the needs of social development. In China, the disease spectrum is changing as in developed countries. It is only because China is a vast territory with large economic and cultural differences among different regions that different kinds of diseases will co-exist for a time. Therefore, we shall continue to study both the drugs for prevention and treatment of various infectious diseases, especially the anti-tuberculosis and anti-AIDS drugs, and the drugs for prevention and treatment of various heart, brain, and diabetic diseases. Additionally, we shall set about to study the drugs for the prevention and treatment of various mental diseases, such as neurasthenia, anxiety, depression, severe psychosis, behavior problems in children, alcohol and drug abuse, senile mental diseases, and psychological disorders in students such as suicide.

Secondly, we shall make the effort to follow the advancement of the forward branches of learning, especially molecular biology and neurobiology. Before the arrival of the post-genome era, based on structural genomics and developments from functional genomics to disease genomics, we shall carry out the timely exploration of drug genomics.

Thirdly, we shall fully utilize the achievements of new high technology. With respect to research and development of new drugs, new high technology such as computer-assisted drug design, combinatorial chemistry, and group screening, high throughput screening has been established in some laboratories in China. At the same time GLP, GCP, GMP, GDP, and GSP systems have been implemented in research and development of new drugs in some cities in China. Simultaneously with full utilization of new High technology, we also shall improve further the research on traditional Chinese medicine and gradually modernize Chinese drugs. At first, we shall introduce international standards into a series of works such as ensuring high quality green medicinal material, implementation of the GAP system, and development of modern dosage forms. In considering the concrete varieties entering the international market, we shall take the intractable diseases as the target and select first to develop the complex prescription of Chinese drugs effective for the diseases that cannot be treated with Western medicine.

The reason for such consideration is that Chinese drugs really have their advantages in treatment of the intractable diseases. We often do not know how to set about the treatment of intractable diseases with Western drugs when the mechanisms of the diseases are unclear. However, Chinese drugs can be used for treatment based on overall analysis of symptoms and signs, while they are obviously present, without need for knowing clearly the mechanism. It is difficult to screen Western drugs because usually there is no animal model for the intractable diseases, while the Chinese drugs can be tried directly on the human body without need for an animal model.

Since the intractable diseases are often related to multiple regional pathological changes, Western drugs are difficult to be effective because they usually focus selectively on a single target. The complex prescriptions of Chinese drugs may be effective because most of them act on multiple targets. Cats are considered good cats if they can catch rats no matter if the cats are white or black. Among ten thousand things, therapeutic efficacy is first. Regardless of this level or that level, the solution of problems demonstrates the real level of ability. Chinese drugs certainly have promising prospects if they can be modernized.

We consider that the research on new drugs is an important area in which to develop collaboration with American colleagues. China has both the experience of a long history, which can be used for reference, and support by modern medical theories and technology. With the rich medicinal resources and excellent quality of professionals in China, we believe that under the circumstances of reformation and opening, we shall collaborate with the scientists of various countries to push the undertakings of research and development of new drugs in China to a new height and to create a new brilliance.

Session I: (continued)

HAN Ji-Sheng: Acupuncture: from pain relief to treatment of drug addiction

Acupuncture is a component of the health care system of China that can be traced back for at least 2500 years. The ancient technique of inserting a metallic needle into the skin and manipulating in a sophisticated and mysterious way has now largely been replaced by electrical stimulation applied on the needle, entitled "electroacupuncture (EA)". The intensity, frequency and pulse width can be identified precisely. The electrical stimulation can also be administered through surface electrodes applied on the skin over the "acupoint" and got very similar results. The device is entitled "Han's Acupoint Nerve Stimulator, HANS". These findings greatly facilitate clinical application and for the study of its mechanisms of action.

It has been made clear that EA is capable of mobilizing the release of opiate-like substances in the brain, entitled enkephalin, endorphin, endomorphin and dynorphin. While EA of low frequency (2 Hz) triggers the release of enkephalin, endorphin and endomorphin (the agonists for mu and delta opioid receptors), 100 Hz EA accelerates the release of dynorphin (the agonist for kappa Opioid receptor). In order to accelerate the release of all 4 kinds of opioid peptides, one can use a specific mode of stimulation, called the dense-and-disperse (DD) mode, where 2 Hz is programmed to alternate with 100 Hz automatically in a certain time interval. This clear finding of frequency-dependent release of central neuropeptides is of scientific importance not only for clarifying acupuncture mechanisms, but also contributes to modern neuroscience, since this is the first report to demonstrate that activities of central peptides can be controlled by electrical stimulations applied at peripheral sites. HANS is very effective for the treatment of low back pain, migraine, muscle spasm and many other painful disorders in the clinical practice.

On the other hand, when the EA is extending too long (lasting for several hours) or used too frequently, the brain will produce anti-opiate substances, such as cholecystokinin (CCK), that works against the opioid peptides to counteract the analgesic effect of EA. Thus the efficacy of EA analgesia depends, among others, on a balance between the relative potency of opioid and anti-opioid substances in the central nervous system. This is probably a good sample of the famous "Yin and Yang balance" theory that forms the backbone of the ancient Eastern philosophy.

In the recent decade it was found that EA could also be used for the treatment of heroin addicts with high efficiency. Animal and human studies revealed that EA of high frequency (100 Hz) is very efficient to suppress the withdrawal syndrome (physical dependence), whereas that of low frequency (2 Hz) is very effective to reduce craving (psychic dependence). It is a common place that drug abuse has become a serious social problem world wide, and there is so far no clue to stop the use of drug. A temporal abstinence is possible during the period of detoxification, but 95% or more go back to drug in a month of time. Therefore the use of portable HANS for suppression of

withdrawal syndrome and heroine craving (by self administration of HANS at the designated acupoints) may open a new field of non-pharmacological treatment to combat with the problem of drug abuse.

Session I (continued)

Roger Detels: Establishing Successful Research Collaborations

There are two kinds of considerations for successful collaborations. One involves areas in research and research support, such as in the following categories.

- Determination of prevalence and correlates (risk factors) for specific diseases.
  - Establishing the existence of an epidemic or high endemicity.
  - Measuring the magnitude of disease in specific geographic locations.
  - Identifying biologic, behavioral, and environmental risk factors for disease.

- Intervention studies.
  - Clinical (e.g., treatments).
  - Biologic (e.g., vaccines).
  - Behavioral (e.g., reducing risk activities).
  - Community (e.g., mobilizing community action).

- Elucidation of biologic mechanisms.
  - Molecular.
  - Genetic.
  - Clinical.

- Resource building (e.g., laboratory resources, clinical skills).

- Manpower development (training).

- Workshops.
  - Technical skills building (e.g., laboratory training).
  - Information dissemination.
  - Consensus building.
  - Advisory (e.g., coordinating research findings and informed policy).

Keys to successful collaboration, include such factors as:

- Trust and frank communication.
- Identified mutual benefits to both parties.
- Priority and relevance for host country.
- Clear lines of responsibility and authority.
- Mutually agreeable policy on publications, patents, etc.
- Cultural sensitivity and awareness.
- Respect for local requirements and regulations.
- Understanding of needs of individual investigators.
- A 'savvy' collaborator.

Session I (continued)

Phil Taylor: National Cancer Institute Intramural Experience in Collaborative Cancer Prevention Research in China

This presentation provides two examples of collaborative cancer prevention studies in China followed by a presentation of issues raised for collaborative research. The two research studies were *Nutrition Intervention Trials* in Linxian and *Early Detection of Esophageal Cancer* also in Linxian.

The two graphical tables below summarize *design* features and *results* for Nutrition Intervention Trials.

Linxian Nutrition Intervention Trials - Design

	Dysplasia Trial	General Population Trial
Population:	**3,318 adults 40-69y, cytologic dysplasia**	**29,594 adults 40-69y**
Design:	**2-arm, double-blind, placebo-controlled**	**½ x 2 x 4 fractional factorial, double-blind, placebo-controlled**
Intervention:	**26 vitamins, minerals**	**Multiple vitamins, minerals**
Duration:	**6 y**	**5 ¼ y**
Endpoint:	**Esophageal cancer incidence and mortality**	**Esophageal cancer incidence and mortality**

Linxian Nutrition Intervention Trials - Results

Dysplasia Trial	General Population Trial
Nonsignificant reductions in:	Significant reductions for beta-carotene + vitamin E + Se for:
• Total mortality (7%)	• Total mortality (9%)
• Total cancer mortality (4%)	• Total cancer mortality (13%)
• Esophageal cancer mortality (16%)	• Stomach cancer mortality (21%)
• Stroke (38%)	• Stomach cancer incidence (16%)

The second study was a set of trials, *Early Detection of Esophageal Cancer*. *Design* and *Results* are summarized in the four charts below.

Early Detection of Esophageal Cancer

- Primary screening for precursor lesions and early cancers
- Localization of precursor lesions and early cancers
- Staging of early cancers
- Endoscopic therapy for high grade dysplasias and early cancers
- Chemoprevention for low grade dysplasias

The Mucosal Staining Study Results

Visibility of High-Grade Squamous Dysplasia (HGD) and Cancer (CA)
(225 patients, 508 biopsy sites, 94 HGDs, 20 CAs)

Before staining:

- Sensitivity of visible lesions for HGD or CA= 62%
- Specificity of visible lesions for HGD or CA = 79%

After staining:

- Sensitivity of unstained areas for HGD or CA = 96%
- Specificity of unstained areas for HGD or CA = 63%

88% of the HGDs and CAs were larger or more clearly defined

Endoscopy Therapy for Early Esophageal Lesions - Available Techniques

Excisional methods:

- Lift and cut
- Banding
- Endoscopic mucosal resection (cap, overtube)

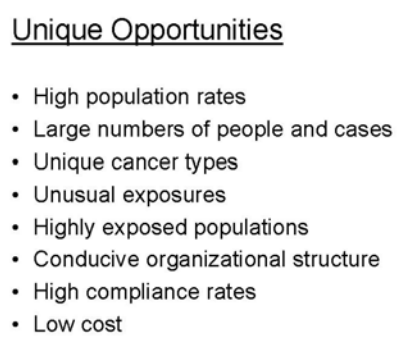
Ablative methods:

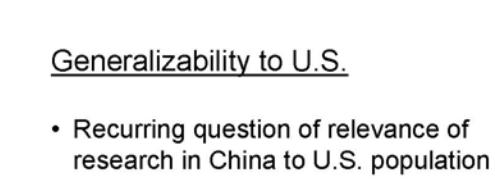
- Bipolar coagulation
- Argon plasma coagulation
- Laser coagulation
- Photodynamic therapy

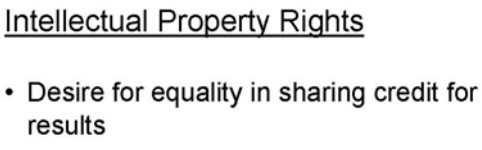
Endoscopic Therapy Patient Follow-up (at 8-20 months, 1996 and 1998)

Endoscopic Therapy	Success rate
Bipolar coagulation only	2/6 (33%)
Argon plasma coagulation only	14/32 (44%)
Endoscopic mucosal resection only	14/19 (74%)
Endoscopic mucosal resection + argon plasma coagulation	1/3 (33%)
Total	31/60 (52%)

Four categories of issues were presented.







Four types of barriers for collaboration were raised.

Physical Barriers

- Communication (language)
- Distance
- Transportation

Regulatory Barriers

- Genome regulations
- State Drug Administration
- Customs Administration

Cultural Barriers

- Blood as a vital resource
- Medical culture based on case reports
- Low autopsy rates
- Differences in personal interactions
- Lack of tradition for individual consent

Infrastructural Barriers

- Limited expertise in design and analysis
- Limited resources
- Communications
- Cost accounting systems

Session II.

WANG Xiao-Min: Telemedicine in China

Telemedicine is about the use of IT — information technology — in health care. The are three major features of telemedicine in China that I will discuss, telediagnosis, teleconsultation, and distance education. All three are encompassed in the China Golden Health Network (CGHN) project.

The CGHN project started in 1995, aiming to link China's hospitals by networks to share the resources and doctors' experience for patients anywhere in the country. The China Golden Health Network is a medical information network, which integrates the most advanced technology and equipment in the field of computer, communication, and medical treatment, and combines the sky net (the specialized Satellite Network) and the ground net (the Internet) together. It has laid a good foundation for sharing the medical information and has promoted the digitizing process of medical information in China.

One of the functions implemented is telediagnosis. Those who need a telediagnosis should apply for it through their doctor in Golden Health Telemedicine Centers. Experts then diagnose the patients from distance via Golden Health Specialized Satellite network, and give advice on diagnosis and treatment. Types of Telediagnosis include:

- Real-time Interactive Telediagnosis, general diagnosis, nominated diagnosis, joint diagnosis, emergency treatment, and so forth.

- Non Real-time Telediagnosis, diagnosis based on patients' case history, image data, and pathological microtomes.

Applicable Targets of the Telediagnosis are the difficult and complicated cases where telediagnosis can provide special expertise or experience to help to diagnosis correctly and give advises on treatment and operation. The merits of Telediagnosis are to make a full use of the medical resources of those national-grade hospitals and to try to solve the unbalanced distribution of the health resources in our country.

The present situation of Telediagnosis consists of the 70 telemedicine service centers all over the China that have been built, the more than 5000 experts registered in our network, and the 10,000 patients involved in all kinds of Tele-diagnosis

Teleclinics provide real-time interactive communication between doctors and patients (without local doctors accompanied). All of our online doctors in this program are well-know experts in China. This is a necessary supplement for telediagnosis

The Golden Health program also provides consultation by experts via Website, what we call teleconsultation. Subscribers can get the medical advices from the online doctors through BBS and email in CGHN website.

CHINA TELEMEDICINE JOURNAL is a part of the Golden Health program, also. It is the first and only academic magazine in the field of Telemedicine in mainland China, and is issued to the whole health stuff in China. It is directed by the information office of Ministry of Health, and is run by Golden Health Medical Network Co. Ltd. In this magazine you can get an idea about the development of the Informatization Project in the field of Health in China — the Golden Health Project, and also know some practical cases of Telemedicine services and distance education in China, the development of the hospital information management, the related policies and laws of Telemedicine services in China, and so on. It also provides a studying and discussing place for those interested in Telemedicine. This bimonthly magazine was firstly issued in August, 1998 in both printed and electronic versions.

The following two cases are examples of accomplishments through the Golden Health Network Project. In one case, seven well-known doctors held a telediagnosis for 12 patients in Klamayi city of Xingjiang Province through Golden Health Satellite Network, which is under authority of Chinese Ministry of Public Health. Participating experts included: Professor Wang Bao-En (Honorary Chairman of Chinese Society of Liver Disease), Professor Tao Qi-Min (Director, Hepatic Institute of Beijing Medical University), Feng Bai-Fang (Vice Director, Hepatic Institute of Beijing Medical University), and infectious disease experts who are Professor Wang Jun-Tao, Doctor Xu Dao-Zhen, Doctor Chen Ju-Mei, Professor & Doctor Tan Yong-Kang. This long distance diagnosis has been proved to be very effective and successful.

In the second case, four famous Beijing neurosurgery experts considered the case of a 12-year old girl, Bai Xue. The patient's sight was threatened and the local doctors were uncertain about the case. Following a telediagnosis, the neurosurgery experts were able to prescribe a new treatment as an alternative to surgery that reduced the tumor causing the problem and was restored to good health, a successful conclusion to telemedicine's mission.

Since the commencement of the CGHN, there has been about one thousand cases got diagnosed from distance. The online hospitals, experts and patients all sing praise for it. Many successful stories spread all over the country, such as a hardly-breath infant, a woman who can neither walk nor sleep, a nearly paralytic young girl, a little girl going blind because of encephalic tumor, a little boy who was facing amputation with serious osteomyelitis, and so on, all these patients got recovered through the telediagnosis of Golden Health Network.

The Development of Distance Education of Golden Health

Cooperating with Chinese Medical Association and many other famous medical educational organs and scientific research institutions, we have developed a real-time interactive distance education via Golden Health Satellite Network for those teachers and students who are far away from each other. In this way numerous medical technicians can get "new information, new theories, new knowledge, new technology and new approaches" in time. Distance Education of Golden Health has low investment, wide

coverage, and numerous beneficiaries, and its teaching program can meet different needs from different levels. Moreover, the fee for those students involved in it is also quite low. Therefore it is regarded as a major means for continuing medical education, which can bring many social and economic benefits. This brand-new teaching form can solve the problem of skew distribution of medical educational resources in China, train the medical staffs at the basic levels, and bring up some cross-century backbones and guides in the filed of medicine.

Abundant Medical Educational Resources: CGHN gets thousands of famous medical experts together, who have extensive theoretical knowledge, rich clinical experiences and high teaching standard, providing sorts of distance education for various major students with the first-rate content and equipment.

Advanced Telecommunication Technology: Via the specialized satellite network, the trans-regional, interactive, real-time, and digitized communication system combining the satellite TV broadcasting and computer data transfer, students can communicate with teachers face to face as if on the scene. They can also make an inquiry about studying content from the distance education system on the Internet website. Lectures are presented in three ways:

- Real-time Interactive Way. Depend on the satellite ground stations and the visual-frequency conference system to realize the real-time, interactive teaching.
- Real-time but not interactive Way. Broadcasting multimedia teaching program made beforehand via the satellite ground station and visual conference system.
- Interactive but not real-time Way. Depending on the internet website to develop the distance education activities, including WWW services, email services, medical educational database, BBS and so on.

Analysis of National Medical Workers Statistics:

1. hospitals: 60,000
2. medical personnel: about 5 million
3. senior medical personnel: 2 million
4. Intermediate medical personnel: over 1 million
5. Nurses, chief nurses: above 1 million.

The preceding was prepared from notes taken at the Forum and from <http://www.2919.net/jw/english/>.

Session II (continued)
William K Michener: Technologies for Understanding Biocomplexity in the Environment

ABSTRACT: At least five related technologies are contributing to our understanding of biocomplexity in the environment. These include: (1) new or enhanced data acquisition technologies; (2) communications and networking; (3) advanced applications; (4) data archives; and (5) tools for knowledge generation and dissemination. Massive data streams are resulting from new and miniaturized in situ sensors, global remote sensing efforts (e.g., the Global Terrestrial Observing System), and hyperspectral sensors. Wireless technologies play an increasingly important role in communicating in situ sensor data from remote locations, greatly enhancing our ability to "instrument the environment." Extensive high performance networks such as Internet 2 and STAR-TAP are now available and are contributing to the exchange of data and models, as well as intersite to international scientific collaboration. Increasingly, environmental science is conducted over the Internet and new, advanced applications are emerging. Examples of the types of applications that will enable us to better understand biocomplexity include new collaborative visual environments (e.g., CAVE), the Collaboratory for Microscopic Digital Anatomy (i.e., Web-based telemicroscopy), and biodiversity workbenches (e.g., Species Analyst). Data archives are beginning to be fully incorporated into the environmental sciences. New software that facilitates data management for ecologists as well as serving as a front-end to a data archive facility is near completion as part of the Knowledge Network for Biodiversity. Metadata clearinghouses are increasingly used for data discovery and documentation purposes. Finally, Web portals and the Access Grid are changing the ways we perform science by greatly enhancing our ability to rapidly generate and disseminate knowledge. These five technologies will support ecologists and other biologists as they continue to expand their scientific worldview (spatially, temporally, and thematically) and address mechanisms underlying biocomplexity in the environment. Some key future challenges include: lack of communication and networking infrastructure in many areas, bandwidth limitations, lack of training in emerging technologies, and need for international standards (e.g., metadata standards, data compatibility, etc.)

PRESENTATION: As part of the policy forum that discusses new technologies that facilitate cooperation, I would like to address several technologies that can enhance our understanding of biocomplexity in the environment. In particular, there are five types of technologies that will be briefly discussed, followed by a summary of some future opportunities for collaboration.

The five types of technologies addressed are:

- Data acquisition.
- Communications & networking.
- Advanced applications.
- Data Archives.
- Knowledge generation and dissemination.

Data acquisition technology includes new sensors and sensor arrays, as well as increasing miniaturization of sensors, enable us to monitor climatic, hydrologic, and biotic conditions at unprecedented scales of resolution, including the physiological monitoring and spatial tracking of individual organisms in the environment. In addition, advances in remote sensing capabilities, including the various programs of the U.S. Geological Survey's Earth Resources Observing System (EROS) <http://edcwww.cr.usgs.gov> are allowing us to map land cover and monitor land use change at global scales. Increasingly, we can monitor aspects of environmental health at frequent time intervals and broad spatial scales. Data and images like one displaying an estimate of land gross primary production for the United States over a two-week period in the spring of this year, can be found at the data center at the URL above. Regional to continental to global scale monitoring still requires that satellite sensor data be related to what is actually present on the earth's surface. An example involving China involves data from the Beijing Forest Research Station being used to verify land cover data derived from satellite sensors as part of the Global Terrestrial Observing System (GTOS) pilot project that is part of EROS.

Advances in hyperspectral data acquisition (i.e. 200 or more bands of spectral data acquired simultaneously) offer the ability to actually begin to discriminate land cover to the level of tree species. Our ability to collect massive amounts of environmental and other types of data has necessitated the development of the communications and networking infrastructure that is necessary to transmit those data.

For instance, broad-spectrum wireless communication supports automated environmental monitoring in remote areas. Here, water quality data are being remotely collected at variable depths and then transferred via wireless communication to the onshore laboratory at the North Temparate Lakes LTER (Long-Term Ecological Research) site in Wisconsin. Extensive high performance networks, such as Internet 2 and STAR TAP are available and useful for facilitating scientific data exchange, model simulation, communication, and teaching. There are two Internet2 backbone networks, the vBNS developed by MCI Worldcom and the National Science Foundation, and Abilene, developed by the University Corporation for Advanced Internet Development, Qwest, Cisco and Indiana University.

Vast improvements in communications have led to a rapid rise in the number of people using the Internet. Projections of numbers of people using the Internet worldwide show a rise from about 35 million in 1995 to nearly 350 million — an order of magnitude increase — by 2005. The figures are probably very conservative. Advances in communication and networking also support advanced scientific applications.

Tele-cubicles and Collaborative Virtual Environments (CAVEs) are different interfaces used for some advanced applications. Immersion in a virtual world, or interaction among people using these interfaces allows people to interact with applications in new ways. But the requirements of network applications using these kinds of displays generally require

advanced networking. For example, web-based telemicroscopy allows users at remote locations to access advanced electron microscopes for sample analysis.

The "species Analyst" workbench and related software (developed at the University of Kansas and the San Diego Supercomputer Center) provide access to museum specimen data and enable the development of predictive models based on species and environmental data, such as the potential spread of an invasive species of insect.

Data Archives comprise one of the major research and development areas is related to establishing easily-accessible national and international repositories for environmental data. One important example is the Knowledge Network for Biocomplexity — a collaboration among the University of New Mexico, the National Center for Ecological Analysis and Synthesis, and the San Diego Supercomputer Center. "MORPHO" represents a software tool that enables data and metadata entry, as well as access to a large mass storage facility.

Metadata Clearinghouses are related efforts include the development of the NBII Metadata Clearinghouse in the United States (for storage and access of information that describe existing databases). The International Standards Organization is currently working on establishing a metadata standard that can facilitate international efforts.

New technologies have the potential to drown us in an ocean of data. Thus, new approaches for knowledge generation and dissemination are needed. Several are available now. Portals provide an efficient and powerful approach for transferring knowledge is through the use of Web portals. One well-known example is the "stke" (the Signal Transduction Knowledge Environment) from Science magazine and Stanford University which provides a single, user friendly portal for news, data, models, and other tools, articles, and other useful information about signal transduction research activities. Portals will not, however, replace the knowledge transfer that occurs in people-to-people meetings. New approaches, though, like the Access Grid enable individuals and groups to meet virtually over the internet — thereby facilitating rapid information and knowledge transfer.

The future holds many opportunities for collaboration. Adequately addressing issues like complexity ultimately requires multidisciplinary and international cooperation. In the long-term, such questions will require continued and substantial improvements in networking and increased international access to appropriate bandwidth. In the short term, international exchanges of scientists and cooperation in developing standards for data collection, metadata, and information management are particularly important to encourage. Training and cross-disciplinary workshops on emerging technologies for environmental sensors, communication, and networking can also facilitate scientific collaborations and, ultimately lead to a better understanding of biocomplexity in the environment.

Session II. CHEN Zhu: The Human Genome Project in China

China is the most populated country in the world (accounting for 22% of world's total) and the Chinese population is composed of many ethnic groups which represents a precious genetic resource for studies on human genome diversity and evolution, as well as for hunting of human disease related genes. The Human Genome Project (HGP) in China was launched in 1994, and has been supported by the National Natural Science Foundation of China, The Chinese High Tech Program (863), and the National Key Research Program (973).

In view of the actual situation, the emphasis has been laid on genomic diversity and isolation of disease genes while taking advantage of human genetic resources. Over the last 5 years, through effort of the whole scientific community, a number of centers of excellence were organized, a nationwide network for collection and preservation of genetic materials established, and a comprehensive genomic research technology system implemented. Among the new technologies introduced and further developed, one can list those for genetic and physical mapping, cloning of human genes, large scale DNA sequencing, mutation detection and bioinformatics. Meanwhile, important achievements have been made in research projects. In the area of genomic diversity, a large number of DNA samples were collected form different populations.

A study on the genetic relationship between 30 ethnic groups in South and North China has been performed and the results were compared with 15 reference populations in the world. It was found through this study that Chinese population could be divided into Southern and Northern ones, that the two populations may originate from the South and that the gene pool of East-Asian population is likely to be derived from Africa.

On the other hand, the study on disease genes has made some progress, including the cloning of a gene responsible for hereditary high frequency hearing loss and the characterization of structure and function of genes associated with leukemias and solid tumors. An initiative has also been made in the mapping of polygenic disease loci. In addition, several groups have made breakthrough in large scale cloning of human functional genes. Over 500 full-length cDNA of novel genes were obtained from hematopoietic precursors, neuro-endocrine tissues and cardio-vascular system.

Recently, attention has been paid to the sequencing of human genomic DNA. Significant progress has been made in sequencing 1% of the human genome (a 30Mb region on chromosome 3P), as a part of the international human genome sequencing consortium. Moreover, the study on some pathogenic microbes such as Leptospira is now being carried out at the National Human Genome Centers and it is estimated that the full genomic sequencing of Leptospira will be finished by the end of 2000. In the future, the analysis of genotype-phenotype correlation should be strengthened in order to uncover the interaction between genetic and environmental factors underlying human diseases. Multidisciplinary collaborations will be encouraged to promote the study on functional genomics. Finally, the HGP in China should be more integrated into the international efforts and the mutually beneficial collaborations will be further promoted.

Session II. (continued)
Elke Jordan: The Human Genome Project in the United States

The Human Genome Project is an international research effort to characterize the genomes of the human and selected model organisms through complete mapping and sequencing of their DNA and analysis of genome function. In addition to creating these datasets, the HGP aims to:

- Develop efficient and high-throughput technologies for genomic analysis,
- Examine the ethical, legal, and social implications of human genetics research, and
- Train scientists who will be able to utilize the tools and resources developed through the HGP to pursue biological studies that will improve human health.

The U.S. component of the HGP, managed by the NIH and the DOE, from the beginning has developed specific goals and timetables, which were published as five year plans. The first plan was for the period 1990-1995, and served to focus the efforts of the research community on the most important initial objectives, namely generating genetic maps, physical maps and improved technology for sequencing. Because progress was more rapid than anticipated, the 1990 plan was updated in 1993 by extending the initial goals and scope of genome research. The new goals were published in Science (Science 262:43-46; 1993).

In 1998 another NIH-DOE 5-year plan was developed to cover completion of the original objectives of sequencing the human genome and to expand the HGP to the study of genetic variation and functional analysis of the genome. This plan was also published in Science. (Science. 282: 682-689; 1998.)

The National Human Genome Research Institute (NHGRI) supports research projects aimed at accomplishing the goals of the HGP at universities and research institutions across the U.S. The development and management of these projects are carried out by the NHGRI's Division of Extramural Research (DER). The DER, with advice from the extramural research community and the National Advisory Council for Human Genome Research, sets the scientific priorities for HGP research and supports and manages the peer reviewed research projects that address these priorities. To date all the goals that were set in the various 5-year plans have been met on schedule, culminating in the publication of the draft human sequence in February 2001.

The HGP in the U. S. has included support for research on ethics from the outset. The Ethical, Legal, and Social Implications program (ELSI) at NIH was established in 1990 by the architects of the Human Genome Project to anticipate and address the ethical, legal and social issues that arise as the result of human genetic research.

For the future, the U.S. program will continue addressing the goals in the latest five-year plans. Several areas are receiving special attention at this time. The human sequence still needs to be completed, which is anticipated by 2003. A number of additional organisms will be sequenced, including the mouse, the rat and the zebra fish. Sequence from these organisms will be indispensable for the study of genome function. Human DNA sequence variation is also being studied intensively, including how sequence variation affects phenotypic traits. Support for development of the bioinformatic tools and computational strategies needed for the collection, analysis, annotation, and storage of the ever-increasing amounts of DNA mapping and gene expressing data is a high priority. In the ELSI area some of the emerging areas are the issues around the study of genetic variation among groups, how the concepts of race and ethnicity relate to genetics, and the increasing use of genetic information in health care and in the workplace.

Session II. (continued)
HONG Guo-Fan: Rice Genomics — Achievements and Plans

Structural Genomics of rice.

1. The Bac-fingerprinting map of (Indic) rice genome is available.
2. Indica rice chromosome 4 sequencing will be finished in the next year.
3. The comparative sequence analysis will be performed between indica and Japonica. The available maps and sequences of the two varieties should facilitate this type of study.
4. A rice transcription map of different tissues, organs and at different developmental stages is now under way.
5. Genes of agronomic significance may be identified by comparing with the transcription map of the target rice .
6. Identification of other cereal genes of interest using the colinearity of both molecular markers (anchor set) and the genes between rice and other cereals such as corn, wheat etc.

Functional genomics of important agronomic traits in rice.

Genes essential for agronomic performances of crops can be utilized to further benefit food production and quality through genetic engineering. In this program, genes related to flowering, plant architecture, fertility, reproduction and metabolic controls in rice will be identified through a combinatorial approach of genetics, molecular biology and functional genomics. Two major aspects of this program are mutant screening and identification and gene isolation using high throughput technology. Both EMS-induced and insertional mutants by transposons and T-DNA will be produced at a large scale. To isolate as many genes as possible, gene expressional profiles will be established and compared by microarray technology. In this way, key agronomic genes controlling the quantity and quality of rice grains will be tracked down.

1. Research targets for a five year period.

1.1 Generate 2000 transposant lines containing transposon insertions and accomplish genetic analysis of 50-100 mutants related to rice developmental and metabolic controls;

1.2 Construct 1-2 normalized rice cDNA libraries, obtain 10000 EST, establish expressional profiles of genes related to the biological processes of interests and further identity key agronomic genes in combination with gene functional analyses;

1.3 Establish a bioinformatic database for rice genes;

1.4 Isolate 40 full-length genes involved in controlling agronomic important traits;

1.5 Train young scientists to be highly qualified in the fields of molecular biology and modern crop breeding;

1.6 The findings from this program will eventually pave the ways for crop improvements by genetic engineering.

2. Recent results

2.1 Mutant Generation

Over 10 rice monogenic mutants affecting several aspects of vegetative and reproductive developments have been fully characterized and the genes affected are being cloned by a map-base approach. These mutants were derived form both japonica and indica varieties. Around 3000 Ds insertion lines have been generated and several mutants identified from a japonica variety.

2.2 cDNA library construction

Over 10 full-length cDNA libraries have been constructed from youg seedlings, shoot apical meristems, pollinated pistils, embryos including fertilized eggs and leaves challenged by pathogens. The material were derived from both indica and japonica varieties. The libraries are being normalized by a cDNA array procedure and the unigenes are being sequenced. We plan to obtain 10000 rice unigenes. This information will be utilized to produce microarrays for expressional profiling of genes related to rice grain quality.

2.3 TAC library

Two indica TAC (transformation-competent artificial chromosome) libraries have been constructed: one with an average insert length of 45 kb and the other 85 kb. TAC contigs for two genes influencing fertility have been constructed and single TACs containing the target genes identified.

3. International collaborations

We seek to share our data with people working on rice functional genomics, in particular, the rice unigenes, expressional profiles and mutant resources and hope to establish an international platform for rice genomics.

Session II. (continued)
Mary Lou Guerinot: Nutritional Genomics

Nutritional genomics is about manipulating plans to improve human health.

- Works at interface of plant chemistry, biochemistry, genomics and human nutrition
- Plant foods contain almost all the minerals and organic nutrients established as essential
- Fortifying foods before harvest.

Issues:

- Crops that benefit the farmers that grow them, but, as such, do not offer added value for the people who consume them vs. added value for consumers.
- Input traits vs. Output.

Vitamin A

- Improved vitamin A nutrition could prevent 1-2 million deaths each year among children aged 1-4 years.
- Rice grains with beta-carotene.

An example of addressing the global problem of Vitamin A deficiency as a global problem is Golden Rice, featured as a cover story in Time Magazine (Vol. 156, No. 5, July 31, 2000). Golden Rice is a transgenic phenomenon with the gene of a butterfly inserted into rice. It enriches the beta-carotene in rice that is transformed into Vitamin A by humans.

We need to understand how plants acquire minerals.

- Improve plant growth.
- Improve crop yields.
- Improve animal and human nutrition.
    - Sustainable problems of malnutrition.
- Utilize marginal soils.
- Remediate soils.

Iron

- Iron deficiency is the most common human nutritional disorder.
- Most people get their iron from plants.
- Iron is one of the three nutrients that most commonly limit plant growth.

Selenium.

- Anti-carcinogenic properties.
- Certain plants naturally hyper accumulate selenium.

Potential Problems.

- Allergens (e.g. introducing new ones).
- Some vitamins and minerals have upper limits of safety.
- Patents — there are about 70 different patents tied up in golden rice.
- Deciding which foods to fortify, and who gets to decide?

Potential for Edible Vaccines.

The 2010 Project

- To know the function of every gene in the arabidopsis genome by 2010.
- 25,000 genes.

Session III: Biodiversity and Ecology of Infectious Diseases

JIANG Zhigang: Wildlife Conservation in China: Policy, Practice and Prospects

China is a country rich in biodiversity with its fauna characterized by endemic species, China has about 11.5% of the world mammal species, 13.5 % of the world bird species, 6.7 % of world reptile species and 6.8% of the world amphibian species. China is also the largest country in the world by population, which puts enormous pressure on its limited resource. Despite of this problem, China has made impressive stride towards saving its wildlife in recent two decades. Since the reform movement in China in late 1970s, China has made many legislatures in the field of natural and wildlife conservation, even though in order match the changed natural and legal environments some of the laws are needed to be revised.

The country also became a party of many international conventions and bilateral, multilateral environmental treaties, including the Convention on Biological Diversity, Convention on International Trade in Endangered Species (CITES) and RAMSA treaty. Much effort has been dedicated to the in situ conservation. China has established more than 1000 natural reserves to protect the endangered wildlife and its habitat, as well as important and vulnerable ecosystems. Those reserves have covered over 8% of the territory of country. But China lacks the financial and human resources to effectively protect all the habitats of species in needs of protection.

At the same time, China has established 14 wildlife rescuing and breeding centers and 7 wildlife parks. Many rare and endangered species such as giant pandas, Przewalski's, Yangtze, crested ibis, and tigers were surviving in ex situ conservation. Chinese scientists in collaboration with their foreign colleagues carried out many surveys, expeditions on wild fauna, Biodiversity and endangered species inventory and information system have been set up in the country. The Red Data Books of Chinese Endangered Animals was published in 1998 and Chinese scientists are compiling Fauna Sinica. Wildlife NGOs and media opened other frontier in the wildlife conservation campaign; they worked side by side to improve the public consciousness of environment. At the same as China matches with the step of world community to implement CITES and Convention on Biological Diversity, the medicine research and administrators are searching for substitutes for the traditional Chinese medicines. The policy, practice, problem and prospects in China wildlife conservation are outlined in the paper. Here, I also present special case studies for the conservation of crested ibis, giant panda, tiger, Père David's deer, and Mongolian gazelles.

Session III. (continued)
ZHU Zuoyan: Gene transfer in fish and the biosafety

Based on the technique of microinjection, first batch of GH-transgenic fish was produced in China and a model of transgenic fish was then established. The “all-fish” GH-transgenics not only grew faster but also were more efficient in utilizing dietary protein than the controls. Meanwhile, the transgenics had significantly higher body contents of dry matter and protein, but lower content of lipids than those of the control. Sterile of triploid transgenic common carp were successfully produced, which are safe for the water-ecosystem. Two groups of mice, fed with “all-fish” GH-transgenics or the control fish, respectively, did not show any significant differences in physiological and pathological characteristics. According to the substantial equivalence of biosafety principle delivered by European OECD (Organization for Economic Cooperation and Development) in 1993, the safety class of “all-fish” gene-transferred common carp could be determined in the “level I”, the safest class.

Session III. (continued)
Joshua Rosenthal: Biodiversity and Human Health

What is Biodiversity ?

- " … the total variety of life on earth. It includes all genes, species and ecosystems and the ecological processes of which they are a part." (ICBP 1992)
- 'the variety and variability of life on the planet.'

Non-human biodiversity is important to human health in at least four broad areas. These include:

- Drug discovery from natural products,
- Biology of disease vectors (ecology of infectious diseases),
- Biological indicators & modifiers of environmental quality,
- Numerous topics that use non-traditional organisms to model human systems.

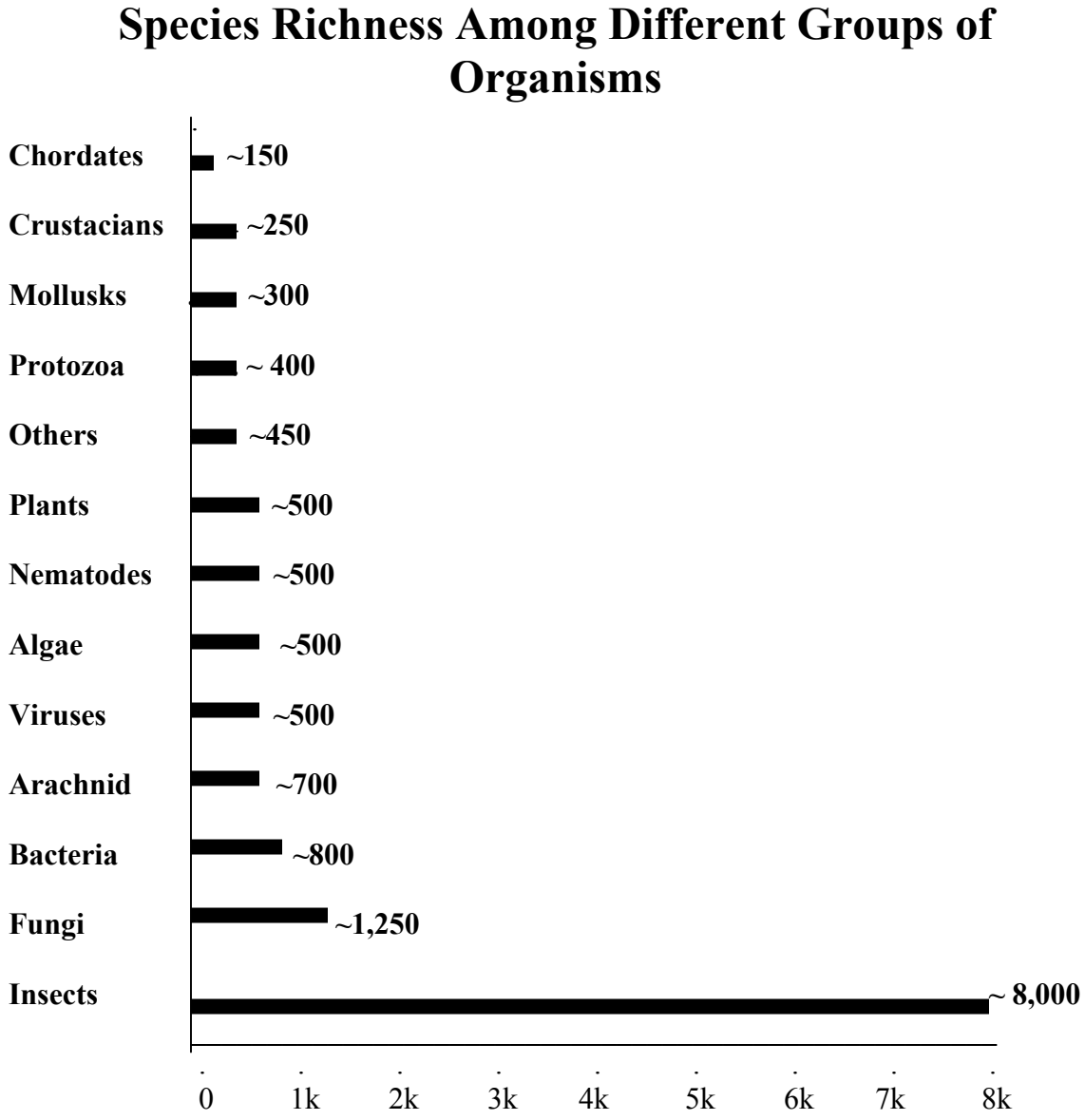
All of these medical areas benefit from an expanding knowledge base in the biodiversity sciences, and all appear to be experiencing increased interest from the academic or industrial sectors of the United States.

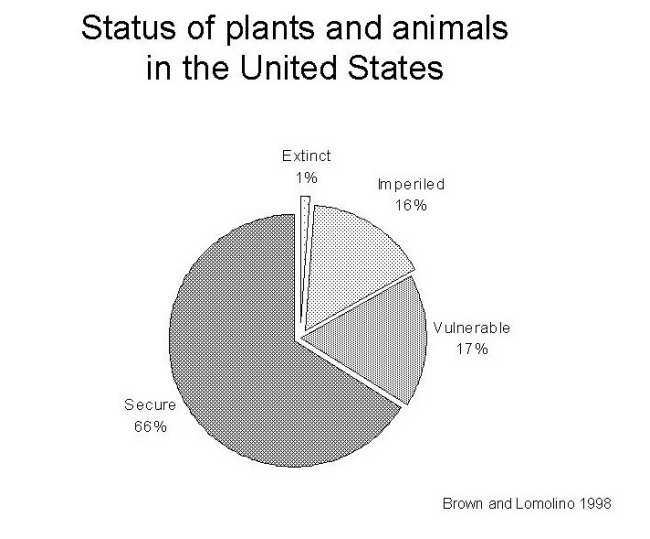
In addition to first-rate biomedical research, I believe that there are several important conditions that will enable advances in sustainable use of biodiversity in these areas. From a scientific standpoint, advances require excellent understanding of the systematics and taxonomic identity of organisms, as well as up to date knowledge of their geographical and ecological distributions.

The following table and charts are indicators of the range and scope of this endeavor:

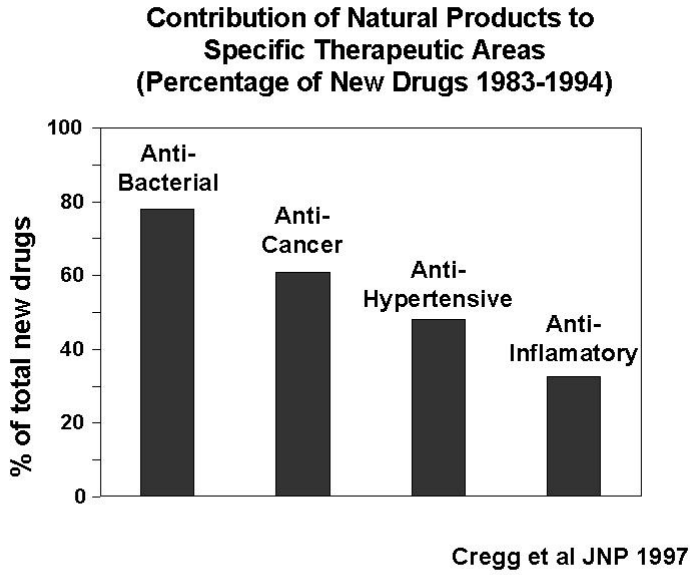
How many species exist?

- 1.7 million species have been described.
- Estimates range from 3.5 million to 111.5 million species globally.
- Conservative "working estimate" — 14 million (Haywood 1995).


Species Richness Among Different Groups of Organisms
Chordates
~150
Crustacians
~250
Mollusks
~300
Protozoa
~ 400
Others
~450
Plants
~500
Nematodes
~500
Algae
~500
Viruses
~500
Arachnid
~700
Bacteria
~800
Fungi
~1,250
Insects
~ 8,000
0
1k
2k
3k
4k
5k
6k
7k
8k


Status of plants and animals
in the United States
Extinct
1%
Imperiled
16%
Vulnerable
17%
Secure
66%
Brown and Lomolino 1998

This rapid loss of global diversity, especially in developing countries, is under particular threat from economic development activities. One of the serious consequences is the loss of natural products as sources of new medicines.



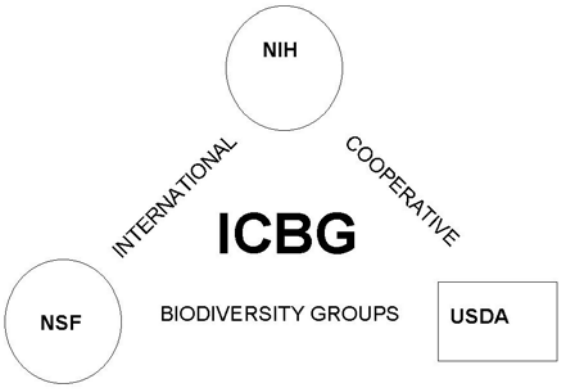
Some examples of research projects funded by NIH toward discovery of new medicines from biodiversity:

Natural Products Drug Discovery

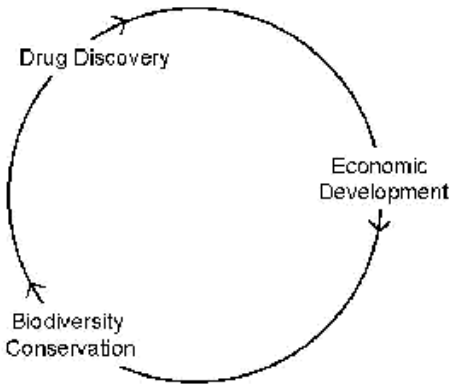
- Anti-mycobacterial Agents from Higher Plants (NIAID)
- Caribbean Corals (Pseudopterogoria) as a Source of New Anti-inflamatory Agents (NIGMS)
- Structure and Function of Snake Venom Glycoproteins (NCI)

In addition, access for scientists to those studies and the resulting data are critical. In this context, I will mention several global and regional initiatives, including Species 2000, the Integrated Taxonomic Information System, and the Global Biodiversity Information Facility, that the U.S. supports to help link and verify taxonomic and inventory information on biodiversity.

In part to address these last needs, three agencies of the U.S. Government, the National Institutes of Health, the National Science Foundation and the Department of Agriculture, support an experimental effort to integrate research in natural products pharmaceutical and agricultural discovery with economic development and biodiversity conservation.



International Cooperative Biodiversity Groups
Conceptual Framework



International Biodiversity Group: Program Goals

- Conserve biological diversity.
- Discover natural products for pharmaceutical and agricultural development.
- Promote scientific and economic development in developing countries.

International Cooperative Biodiversity Groups: 1998 Awards

David Kingston	Tropical Rainforest Plants	Suriname, Madagascar
Brian Schuster	Tropical Rainforest Plants	Cameroon, Nigeria
Barbara Timmermann	Arid Lands Plants, Endophytic Fungi	Mexico, Chile, Argentina
Brent Berlin	Highland Plants and Fungi	Mayan Mexico
Phyllis Coley	Tropical Rainforest Plants, Insects, Enophytic Fungi	Panama
Doel Soejarto	Tropical Rainforest Plants	Vietnam, Laos

Studies on Biodiversity of Vietnam and Laos

- Doel Soejarto, University of Illinois – Chicago
- National Center for Natural Sciences and Technology — Vietnam
  - Institute of Biotechnology
  - Institute of Chemistry
  - Institute of Ecology and Biological Resources
- Cuc Phuong National Park — Vietnam
- Research Institute of Medical Plants — Laos
- Glaxo-Wellcome Research and Develoment.

Lastly, the increasingly global nature of biomedicine and biodiversity research efforts requires that we develop clear guidelines for legal access to biological organisms, and mutual understandings regarding contributions to intellectual property and the sharing of benefits associated with their use and development.

This program, the International Cooperative Biodiversity Groups, is guided by a set of clear and enforceable guidelines for the treatment of intellectual property and equitable benefit-sharing.

International Cooperative Biodiversity Groups Research and IPR Agreement Types often involve several interrelated contracts, including:

- Cooperative Research and Development Agreement
- License Option
- Know-how License
- Material Transfer Agreement
- Benefit-sharing Agreement
- Trust Fund.

Session III. (continued)

Jerrold Meinwald: The Chemistry of Biotic Interaction: Can We Benefit from Studying the Chemistry with which Biodiversity Provides Us?

Insects and related arthropods, arguably the most successful animals on earth, are especially adept in the exploitation of chemical mechanisms for such vital activities as attracting and selecting mates, locating food, defending themselves from predators, and a wide variety of other purposes. Elucidation of these defense and communication mechanisms provides deep insight into the emerging field of chemical ecology. It also provides opportunities for the development of new biorational techniques that could prove to be of enormous value in connection with the discovery of new drugs, the control of arthropod-borne diseases, the protection of forests, and the pursuit of sustainable agriculture. The exploitation of discoveries in these areas can, however, also raise perplexing questions in the area of intellectual property rights.

The first step for a chemist concerned with these endeavors is to fully characterize the molecular species responsible for the biotic interaction of interest. This area of natural products chemistry is often particularly challenging, because it is usually necessary to devise an appropriate bioassay by which an isolation scheme can be monitored. In addition, the fact that effective chemical signaling in nature may involve as few as hundreds of signal molecules, while chemists usually require many trillions (10^{12}) of molecules even to characterize known compounds, and much larger quantities to determine the structures and stereochemistry of novel structural types, places a premium on the development of nanomolar or even femtomolar separation and characterization techniques.

Because of the alarming rate of species loss worldwide, the need to study natural products chemistry is now greater than ever. A strong case can be made for the special benefits that can be expected from the establishment of international, interdisciplinary groups to pursue this work. Standing in the shadow of gigantic genomic and proteomic projects, however, natural products research is in danger of losing the modest support it now enjoys. The need for renewing interest in this area, as well as in the closely related discipline of chemical ecology, is urgent. Whether this urgency is perceived and acted upon at the highest policy-making levels worldwide will determine whether this uniquely important area of science will flourish or fade in the 21st century.

Session III. (continued)
SHAO Yiming: Current AIDS Research in China and Potential Future AIDS Vaccine Collaboration for China and the U.S.

After going through the introducing phase in the middle 1980s and slow expansion stage in the early 1990s, the HIV/AIDS epidemic has entered a fast spreading stage in China since the middle 1990s. The estimated number of HIV infection has jumped from 10,000 in 1993 to more than 500,000 by 2000. Without vigorous control measures and swiftly implemented a comprehensive plan , the projected number of HIV infection could in China reach 10 million by 2010.

Chinese government has committed to lead a national campaign involving all sectors of the government and NGOs and mobilizing all aspects of the society to fight the AIDS epidemic. The overall strategy is to put the education first and to reduce the risk behavior in the high risk groups and to increase the general awareness of self-protection in the society. The social intervention approach is complemented and strongly supported by the biomedical intervention approaches including epidemic surveillance, molecular epidemiology, clinical research and vaccine development.

A sentinel surveillance networks involving more than one thousand HIV testing laboratories have been established in various regions of China. The networks have generated large quantity of epidemiological data useful for estimation and monitoring the epidemic. The national HIV molecular epidemiology survey found 7 subtypes of HIV-1 as well as HIV-2 and traced the spread of major strains in various regions of the country. The three major HIV-1 subtypes (B', C and B'/C recombinant) cover 80% people infected in China and therefore have been selected as the prototype of HIV vaccine stains. The full-length genome of the strains have been cloned and sequenced.

Three candidate HIV vaccines have been constructed from them, including virus like particle, DNA and live vector vaccines. The DNA vaccine constructed with synthetic gene technology has substantially improved its expression level in mammalian cells and got strong immune response in animals. The recombinant vaccinia virus vaccine containing HIV gag and env genes has also shown good immune response especially when used as a boost after DNA vaccine priming. The phase I clinical trial is under preparation and will start in one to two years depending on the time needed for approval by the State Drug Administration (SDA).

Through close collaboration between traditional and molecular virologist, a novel HIV vaccine has been designed based on the world's first lentivirus vaccine, the Equine Infectious Anemia Virus (EIAV). The EIAV vaccine has been developed and successfully used in China since early 1980s. Specific mutations are found present in the vaccine strains, but absent in the wild type strains of EIAV. These mutations affect the secondary structure as well as phosphorylatin and glycosylation of the critical antigens. The important information carried in the EIAV vaccine has been translated into the corresponding structure and property of HIV antigen. The protein engineering technique has been used to construct a new generation of HIV vaccines.

Most of the above progress in AIDS research has been made through close cooperation with international scientists, including the US colleagues. Being the largest developing and developed country in the world respectively, China and US not only shared the past collaborative experience, but also have great potential for its future expansion, especially in the AIDS vaccine field. The AIDS epidemic in the developed world is slowing down, but is still in its fast expanding phase in the developing countries. Considering the size of the cohorts needed to show a statistically significance, it becomes more difficult to evaluate low efficacy vaccines in a developed country, but much easier to do so in a developing country. Therefore, the close collaboration between them is crucial. The US has the state of the art technology to improve the design and upgrade the vaccine products. China has good infrastructure and professional teams experienced for clinical evaluation of vaccines. China is also capable of producing large quantity of cheap vaccines was proved successful in providing them to her huge population. A closer collaboration between China and US in the AIDS vaccine field could greatly speed up the process to reach the ultimate goal of an effective and affordable AIDS vaccine for the whole world.

Session III. (continued)
Joshua Rosenthal: Ecology of Infectious Diseases

Abstract: Malaria, Leishmaniasis, Lyme disease, Hanta virus, and Cholera are among the more than 35 infectious diseases that have emerged or reemerged around the world in the past 20 years. Simultaneous with this trend we are seeing unprecedented rates of change in the environment and ecology of non-human biota on almost every continent. Virtually all of the world's terrestrial and aquatic communities and ecosystems have undergone dramatic changes due to biodiversity loss, global climate change and environmental contamination. The coincidence of broad scale environmental changes and emergence of infectious diseases may be accidental, but it appears likely that it in many cases that this coincidence reflects 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 understanding of the impact of various types of perturbation on ecosystems and our ability to model and predict those impacts has grown considerably. However, few of the related advances in ecological science have yet contributed to biomedical research and public health.

In a parallel fashion our understanding of proximate factors that contribute to disease transmission and host-pathogen interactions in the human body has grown tremendously in recent years with greater knowledge of the genetics of virulence and immunology. However, the link back to biotic systems that contribute to population dynamics of disease reservoirs and vectors remains poorly understood.

The National Institutes of Health and the National Science Foundation, in collaboration from the U.S. Geological Survey, the National Aeronautics and Space Agency, and the U.S. Department of Agriculture have initiated an interdisciplinary research program on the Ecology of Infectious Diseases. This program brings together ecologists, epidemiologists and biomedical scientists to elucidate the underlying biology of human-induced changes to the environment, including habitat conversion, climate change, invasion of exotic species, and chemical contamination that may affect disease prevalence in humans. One of these projects involves collaboration with scientists at the Langzhou Medical College, Xinjiang Medical University, and East China Normal University in Shanghai to study the dynamics of Human Alveolar Echinococcus in pastoral communities of West Central China.

Classical Ecology of Infectious Diseases

- "Mites as a Reservoir and/or Vector for Prion Disease" (NIA)
- "Molluscan Faunas and Schistosomiasis" (NIAID)
- "Ecology of Hantaviruses in North American Rodents" (NIAID)

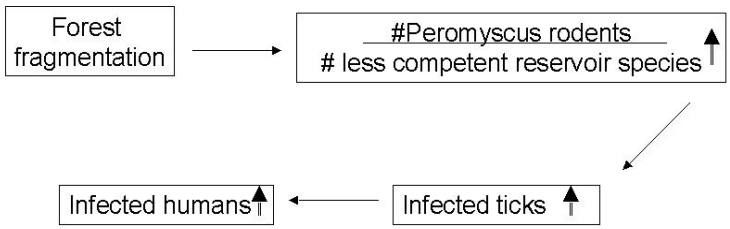
Large scale environmental disruptions that may affect dynamics of infectious diseases

- Human intrusion into forests.
- Fragmentation and reduction of wildlife habitat.
- Introduction of invasive species.
- Hunting and defaunation.
- Agricultural intensification (e.g. increased irrigation or fertilization).
- Climate change.
- Chemical pollutants.
- Dam construction.

Large scale environmental disruptions that may affect dynamics of infectious diseases:

Lyme disease	Leishmaniasis	Filariasis
Malaria	Onchocerciasis	Giardia
Chagas	Schistosomiasis	Toxoplasma
Dengue	Bubonic plague	AIDS
Hantavirus	Cholera	Marburg
Kyanasur Forest Disease	Equine Encephalitis Viruses	Ebola

Lyme disease hypothesis



After Ostfeld 1999

Ecology of infectious diseases:

multivariate

Ecological context

Environmental change

Transmittal agent

Pathogen dynamics

Host biology

interdisciplinary

epidemiology, population ecology, statistics, immunology, parasitology, taxonomy, molecular biology, climatology, hydrology mathematical modeling, veterinary medicine, human clinical research, Remote Sensing- GIS Spatial analysis,

Ecology of Infectious Diseases
A New Initiative by NIH and NSF

Mission: To develop predictive models for the relationships between anthropogenic environmental disturbance and the dynamics of infectious diseases.

Program: Funding innovative, interdisciplinary research programs beginning in August 2000.

Awards:

Thompson Hobbs. Spatial & Temporal Dynamics of Prion Disease in Wildlife: Responses to Changing Land Use [Habitat Fragmentation]

Charles King. Human population growth impact on *Schistosoma haematobium.* [Influence of population and climate changes]

Philip Craig. Parasitic zoonosis (Echinococcosis) transmission in China

Eliska Rejmankova. Environmental Determinants of Malaria in Belize. [Farming intensification and vector populations]

Wayne Getz. Metapopulation Models and Control of TB in African Buffalo

Scott Weaver. Effect of Neotropical Deforestation on Arbovirus Ecology [Dengue Primates and small mammal defaunation]

Stephen McGarvey. Ecology and Transmission of *Schstosoma japonicum*: Philippines

Andre Dhondt. Dynamics of an Emerging Pathogen in an Introduced Host. [Aerially transmitted Mycoplasma in domestic birds]

Linda Lowenstine. Ecology of *Herpesvirus* Infection and Cancer in Sea Lions. [Impact of organochlorine pollutants on immunity and transmission]

David Anderson. Ecology of Virus Transmission in Commensal Bat Colonies. [Rabies and related viruses in relation to urban sprawl]

Joseph Kiesecker. Wetland Urbanization Gradients and Vector-Borne Diseases. [Flatworms in amphibians in relation to urbanization]

Thomas Unnasch. Ecology of Encephalitis Virus in the Southeastern USA[Factors that promote escape from avian hosts to humans]

Parasitic zoonosis (echinoccosis) transmission in Central Western China

- University of Salford (U.K), Sichuan Institute of Parasitic Diseases, Chengdu, Xinjian Medical Univ., Urumqi, East China Normal Univ., Shanghai, and others from France, Ireland, USA and Japan.

- Highly pathogenic tapeworm (*Echinococcus multilocularis*), endemic among Han farming and Tibetan pastoral communities.

- Non human hosts: foxes, dogs, rodents and other small mammals.

- Development of predictive risk models using data from small mammal and human studies in relation to intensified farming and pastoral practices.

Session IV. Clinical Research Systems Compared
KE Yang: Cancer Research in China

As a developing country with a large population, China is a nation of high cancer incidence. In the past decades, the government invested a great amount of funds, labor power and material resource to support cancer research, which has brought on some achievements in prevention, diagnosis and treatment, as well as the basic research in the field. The incidence and mortality of some tumors have decreased. However, with the industrialization and the rapid change of people's lifestyle, the incidence of some other tumors is increasing. The total mortality of cancer is still a leading cause of death. Cancer research remains a baffling medical problem, which needs continuing efforts at present and in a long period of time in the future. Extensive collaboration between Chinese scientists and researchers all over the world in this field should be able to make better contributions in the battle of conquering cancer.

I. The situation and features of cancer incidence in China

The disease and cause of death spectrums in this country have being changed for the past twenty years. Nowadays, cardio-cerebro-vaso diseases, malignant tumors and chronic noncommunicable diseases pose the main threat to people's lives and health. The two retrospective investigations on the causes of death, which were chaired by the State Cancer Prevention Office, indicate that the incidence and mortality of cancer in this country have increased remarkably. The new cases of onset rose from 900,000 per year to 1,600,000~2,000,000 and the death caused by cancer increased from 600,000 to 1,300,000. The general cancer mortality, which used to be 83.65/1,000,000, went up to the second in the range. In the next century, the incidences of most cancers will tend to be ascending with a rate of 1.3% per year within recent period. This means that cancer will still be the most serious public health problem in this country.

In the past 20 years, the incidence of gastric cancer has continuously been the highest one among all the cancers in China. Its new cases maintain more than one third of those in the whole world. The new cases of hepatic and esophageal cancer are a half or more of those in the world. According to the list for incidence of cancers in China, the following tumors continuously occupy the first 6 positions respectively: gastric, lung, hepatic, and esophageal, colorectal, oralpharynx cancer. Breast cancer rise from the 8th position in 1975 to the 6th in 1990. Lung cancer, which was the 6th or 7th in the past, went up to the 2nd or the 3rd. Cervical cancer used to be the 3rd in 1975 and 1980, while in 1985 and 1990, it became the 6th and 9th respectively. The following cancers are estimated to be increasing in a rapid way: lung, pancreas, prostate and ovary cancer, while the incidence of cervical cancer will decrease constantly.

Besides the difference of the composition of cancer in this country, another important characteristic of cancer distribution is the existence of high incidence area and high-risk population in the area for several cancers which represent the natural models for human cancers. In the past several decades, Chinese scientists conducted many epidemiological researches and launched intervention and prevention, some of which were collaborated

with U.S. scientists. Some achievements on etiological epidemiology have been obtained and the improvement of the 5-year survival rate by early diagnosis and treatment are the results of these achievements. It forms a fundamental basis for further research.

II. The features of cancer clinic in China

China has more than 200 cancer specialized hospitals and institutes. The equipments in the hospital and research labs have been greatly improved since 1949, which contributes to the great progress in cancer diagnosis and treatment. In China, clinical doctors have accumulated much experience on the treatment of tumors because they have more opportunities in practicing with large population of cancer patients. The clinical achievements include classifying the level and stage of cancers into grade to guide the treatment and prognosis; improving the entering and the pattern of operations; improving the effect of radiotherapy and chemotherapy. Especially, the whole body regulation concept of Chinese traditional medicine has been successfully integrated into the comprehensive therapy for cancer, which reflect an important characteristic of cancer treatment in China and contribute to the improvement of the 5-year survival rate of several main cancers.

III. The current situation of basic cancer research in china

Most of the research organizations in China distribute in the cancer hospitals and medical universities, the number of researchers focusing on cancer is about 10 thousand. There are also many researchers of other biological medical research institute engaged in the field.

In contrast to other projects, cancer research usually gets more funds from the government every year. The investments of the government are mainly composed of the Fund of National Natural Science, the State “863” Program for High Technology, the State Key “973” Program for basic research and the emphatic basic research items in the provinces, cities or government branches. With the progressing of reform and opening to the outside world, Chinese scientists have started to acquire some risk investment from enterprises. Some researchers have obtained funds from foreign countries. The international co-operations between both governments and scientists are becoming more and more extensive and closer.

The basic cancer research work in China can be classified as followings:

- The etiological research on cancer related to environmental factors, some of which have lead to the research on the mechanism of carcinogenesis in the high incidence fields and in the laboratories.
- Researches on identifying molecular alterations and their association with biological behaviours of cancer.
- The development of new anticancer drugs, biological reagents and the research on pharmacological mechanism.
- Research on biotherapy before clinical trial.

Recently, more mid-age and young researchers who have been trained abroad have returned and entered cancer research organizations. Quite a few of them acquired grants from the government soon. Many of them maintain their collaborations with foreign scientists and initiated their own researches. The gap in basic cancer research between China and developed countries is becoming smaller. The achievements in the cloning of new cancer associated genes and functional studies of them; the research on the mechanism and new ways of treatment on leukemia; the research on nasopharynx cancer and so on are the representative successes of recent years.

IV. Problems and Prospect

As mentioned above, cancer remains the most ferocious enemy to the health of human beings all over the world although cancer research has got great achievements recently due to the investment of the governments and the efforts of scientists. It has been noted that the efforts put on improving cancer therapy are much more than that on prevention, protection for high-risk population and early diagnosis and treatment. In China, The increase of some kinds of tumors reflects the serious environmental pollution brought by industrialization. In many high incidence areas, the incidences of some cancers are still at high level although many intervention and prevention measures have been adopted. Cancer prevention, including research on etiology, epidemiology, screening high-risk population, methods of early diagnosis, is far from perfect in this country.

For further research, great efforts need to be put on improving the quality of basic research and avoiding redundancy; enhancing the co-operations between basic researchers and clinic doctors and among the researchers internationally; setting up better integration between Chinese traditional and Western medicines to develop new ways of treatment and enhancing the high incidence population study to improve effective intervention, early diagnosis and early treatment.

We believe that the success on above aspects will lead to substantial progress, which would contribute not only to China, but also to the whole world.

Session IV. (continued)

Richard L. Mowery: The Organization and Management of Clinical Research at NIH

The NIH is a major sponsor of clinical research. The two major categories of applied clinical research supported by NIH are clinical trials and epidemiology studies. While each Institute and Center at the NIH is responsible for the management of the clinical research it funds, there is a general framework followed by each Institute and Center for organizing clinical trials and epidemiology studies.

For most epidemiology studies, funds are provided to perform the research at the discretion of the person who developed the hypothesis and designed the study. For epidemiology studies addressing high priority areas or are performed at multiple sites, the Institute or Center funding the research may take a more active role in the oversight and management of the study. In some cases, an external Advisory Committee may be established jointly by the NIH and the investigator to provide on-going advice to the investigator and the NIH on the conduct of the study.

The general organizational structure for Phase III clinical trials supported by the NIH consists of:

- A national chairperson responsible for the overall conduct of the trial;
- A coordinating center responsible for data management, data quality and integrity, and statistical analyses; and
- Clinical centers responsible for recruiting and following patients eligible to participate in the trial.

Data and Safety Monitoring Boards (DSMBs) are required for all Phase III clinical trials supported by the NIH. A DSMB is responsible for reviewing accumulated data for evidence of adverse or beneficial treatment effects during the trial and for recommending modification of the trial if necessary. The major responsibility of the DSMB is patient safety monitoring.

Session IV. (continued)
Belinda Seto: Clinical Trial Oversight

The NIH has had a long-standing policy, since 1979, of requiring data and safety monitoring for clinical trials. In 1998, the NIH updated this earlier policy by stating the guiding principles for monitoring (http://grants.nih.gov/grants/guide/notice-files/not98-084.html). Monitoring is commensurate with the level of risk, the size and complexity of the trial. For most phase III trials, a data and safety monitoring board is required. Furthermore, for multisite trials, it is important to establish an effective process for adverse event reporting and communication of the discussion and review of adverse events by the DSMB to the IRB (http://grants.nih.gov/grants/guide/notice-files/not99-107.html).

Recently the NIH has taken new steps to strengthen the oversight and monitoring of clinical trails. These actions include:

- Beginning with the October 1, 2000 receipt date, applicants must submit a monitoring plan for phase I or II trials. The plan is subject to the review and approval of the funding Institute and Center, and awards are contingent on their approval (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html).
- Principal investigators must report certain types of FDA communication to the NIH. These include warning notices and letters, consent agreement and clinical hold letters. Investigators must report to funding IC within 72 hours of receipt. Failure to comply may result in corrective and/or enforcement action. (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-053.html)

Required Education on the Protection of Human Subjects
(http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html)

Beginning Oct 1, 2000, the NIH requires investigators, i.e, key personnel, who are responsible for the design or conduct of research involving human subjects to be educated on the protection of human subjects. To facilitate implementation, the NIH made available a number of ready-to-use curricula, including the intramural computer-based program and a new module developed by the National Cancer Institutes in collaboration with other Institutes and offices. Investigators have some flexibility to determine what is an appropriate level of education. Documentation of education is required before funds are awarded.

Session V. Differences in Chinese and U.S. IPR and Bioethics Systems

YU Xiu-Cheng: The Protection of Intellectual Property Rights (IPR) on Biotechnology (IPR) in China: current situation, problems, and countermeasures.

Concurrent with the ongoing development of its reform and opening-up policy, China has made significant achievement in IPR protection. The legal framework for intellectual property-including patents. Trademarks and copyright were further implemented and perfected in China.

In the meantime, China was earnestly undertaking its international obligations regarding the protection of intellectual property rights. But due to restraints by economic factors, the total level of IPR protection in China is very lower than in developed countries such as in USA.

During the more and more intensive international competence, especially in high biological field, we should learn from other's strong points to offset our weakness, implement our policy and adjust our strategy through wider international exchange and cooperation.

Session V. (continued)
Yang Lincun: Intellectual Property Right Protection of Medicine in China

It is deemed that intellectual property right (IPR) protection is very important to medical and pharmaceutical industries. As a developing country, China has achieved a lot in developing its IPR system within the past decade, but we still have a long way to go. However, we have made rapid progress over the past few years.

□. China has built up a relatively good IPR system.

1. China has promulgated many laws and regulations in field of IPR, such a Patent Act, Trademark Act, Copyright Act, and Trade Secret Act.
2. In field of medicine, China has issued relative good administrative laws and regulations.
3. Up to present, China has signed almost all of the international treaties in field of IPR.
3. We are strengthening very fast about IPR protections in enterprises and research institutes, and enterprises, universities and institutes have been becoming main bodies in IPR protection in China. But,
5. Tortuous phenomena in field of IPR are still serious in China.

□. Several IPR problems in field of medicine field

1. Administrative protections.
2. Relationship between medical registration and patent protection.
3. Regulations relevant to clinical test.
4. Protection to genetic resources.

□. New Problems

1. Problems concerning participation to WTO.
2. Bio-safety of genetic manipulations.
3. Public Order and moral aspects.
4. IPR issues in international cooperation.

Session V: (continued)

Kia Chen: Technology Transfer at NIH

INTRODUCTION

The Office of Technology Transfer (OTT) at the National Institutes of Health (NIH) evaluates, protects, monitors, and manages the NIH invention portfolio to carry out the mandates of the Federal Technology Transfer Act (FTTA). FTTA was enacted in 1986 and encourages the transfer of technology from federal laboratories into the private sector. This is largely accomplished through overseeing patent prosecution, negotiating and monitoring licensing agreements, and providing oversight and central policy review of Cooperative Research and Development Agreements. OTT also manages the patent and licensing activities for the Food and Drug Administration (FDA). In addition, OTT is responsible for the central development and implementation of technology transfer policies for the three major research components of the PHS — the NIH, the FDA, and the Centers for Disease Control and Prevention.

The primary objective of OTT is to ensure that the public derives health benefits from discoveries made by NIH scientists. Another benefit of OTT programs is stimulating economic development by helping both newer and established companies grow around NIH technologies and add product candidates to their pipelines. Through licensing NIH technologies to the private sector, public also benefits from the financial return on public investment in NIH research. Such arrangements also bring financial rewards to NIH inventors for their innovative work through a share in royalty income.

TECHNOLOGY DEVELOPMENT AND LICENSING

Each year, hundreds of new inventions are made in Public Health Service (PHS) laboratories. The Office of Technology Transfer (OTT) transfers these inventions — through licensing to the private sector — for development that will benefit the public health. Often, companies in the private sector require patent protection to justify the expenditure of resources needed to fully develop a particular invention. Where necessary to ensure the rapid and effective development of a particular invention the OTT seeks intellectual property protection (both domestic and foreign) on PHS inventions.

TECHNOLOGY PROTECTION

Upon reporting of an invention to the OTT, a team of OTT Patent Advisors and Licensing Specialists evaluate the invention to assess patentability and probability of commercial success of the invention, as well as the need for patent protection to ensure rapid and effective development of the invention. The OTT generally seeks the broadest possible patent protection for commercially valuable inventions and initiates this process by filing an application for a patent in the U.S. Patent and Trademark Office (USPTO).

Within 12 months of filing a U.S. patent application, the OTT will update its initial patentability and market assessments, and, after consultation with the Institute or Center (IC) that sponsored the research leading to the invention, will file international patent applications as appropriate. In general, where international filing is possible and commercial interest in the invention can reasonably be anticipated, the OTT recommends at least preliminary filing of an international application under the Patent Cooperation Treaty. Approximately one year after the filing of an international application, the OTT again reevaluates the commercial potential of the invention. When appropriate, the OTT files national stage patent applications in those countries where it is believed that patent protection is required for the full development of the invention.

TECHNOLOGY LICENSING

If a company would like to acquire rights to use or commercialize either an unpatented material, or a patented or patent-pending invention developed in PHS laboratories, a license is required. A license is a legal agreement by which the owner of an invention promises not to take action to exclude the licensed party from making, using, and/or selling the invention. Where appropriate, licenses to PHS inventions are granted on a worldwide basis. Most biomedical companies, whether large or small, desire worldwide patent protection to secure foreign markets or to use their assets in establishing strategic alliances which can add to the further development of the invention and the distribution of its benefits to the public.

Types Of Licenses Available

If the invention desired by the company for commercial purposes is claimed in a patent or patent application owned by the U.S. Government, the company must negotiate either a Commercial Evaluation License, an Internal Commercial Use License, a Nonexclusive Patent License or an Exclusive Patent License through the OTT.

Commercial Evaluation Licenses grant the nonexclusive right to make and use the technology for the purpose of evaluating its commercial potential. The license is for a limited number of months and does not grant the right to sell or otherwise distribute the invention. Companies are required to obtain a commercial patent license for further use and/or development of the invention.

Internal Commercial Use Licenses grant the nonexclusive right to make and use the invention for the purpose of internal use by the licensee. These licenses do not grant the right to sell or otherwise distribute the invention, but allow the licensee to use the invention as a tool in their commercial development activities.

Nonexclusive and Exclusive Patent Licenses allow a company to commercialize the invention, under appropriate circumstances pursuant to applicable statutes and

regulations. An exclusive license limits the use of the invention to a single group or entity while a nonexclusive license allows for use by multiple concerns.

If the invention desired by the company for commercial purposes is not claimed in a patent or patent application owned by the U.S. Government, the company must negotiate a Biological Materials License.

Biological Materials Licenses allow a company to make, use and/or sell commercially useful biological materials which are not in the public domain and for which patent protection cannot or will not be obtained. This type of license typically is nonexclusive and facilitates the commercial development of biological materials developed in PHS laboratories without requiring that patent protection be obtained for every material.

How To Obtain A License

A company that desires a license to develop a PHS invention must complete and submit to the OTT an Application For License To Public Health Service Inventions. This application forms the primary basis for licensing decisions. It provides the OTT with information about the potential licensee, the type of license desired, some of the terms desired and the potential licensee's plans for development and/or commercialization of the invention. Also, if the applicant desires a license with some form of exclusivity, the completed application provides the OTT with the applicant's justification for an exclusive license.

After reviewing the license application, the OTT, in consultation with the IC that sponsored the research, determines if the applicant's proposal is consistent with the licensing strategy developed for the invention and whether the grant of the license would benefit the public and be consistent with the interests of the Federal government. If the applicant has requested a nonexclusive license and a favorable determination has been made upon the application by the OTT negotiations will begin as appropriate.

If the applicant has requested an exclusive or partially exclusive license the OTT will publish a notice in the Federal Register, as required by law, and after a 60 day period will reevaluate the application and all comments received from the public to make a final determination regarding the license. The criteria to be considered in evaluating exclusive license applications (37 CFR §404.7) include whether:

- Exclusive licensing serves the best interests of the public.
- Practical application of the invention is not likely to be achieved under a nonexclusive license.
- An exclusive or partially exclusive license is a reasonable and necessary incentive to promote the investment of risk capital to bring the invention to practical application.
- Exclusive or partially exclusive license terms and conditions are not broader than necessary.
- Exclusive licensing will not lessen competition.

Terms Included In The License

The OTT has developed several model license agreements that serve as the basis for license negotiation. The business development plan submitted as part of the license application process serves as the basis for establishing performance benchmarks that are included in the license agreement. The OTT works closely with licensees to monitor performance and to adjust benchmarks, when appropriate, to ensure the successful commercial development of its inventions.

Licensees are required to respond at least annually on their utilization of or efforts to utilize license patent rights. These responses are kept confidential and, to the extent permitted by law, are exempt from disclosure under the Freedom of Information Act (5 U.S.C. §552).

Licenses are revocable for specific reasons, such as non-use of or failure to develop the invention, failure to comply with governing regulations, or failure to satisfy public health needs. Licensees also must normally agree that any products embodying the invention or made through the use of the invention, and which are sold in the United States will be manufactured in the United States.

COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENTS (CRADAs)

What Is A CRADA?

Under the Federal Technology Transfer Act (FTTA) of 1986, Congress created Cooperative Research and Development Agreements (CRADAs) to enhance and facilitate collaboration between governmental agencies and commercial firms. The FTTA provides the authority and an effective mechanism to enter into joint research and development projects.

CRADAs benefit the public by transferring know-how and technology from Government laboratories, thereby encouraging the development of improved health-care products, processes, and services. The FTTA has been embraced by the Public Health Service (PHS), which has a long-standing record of successful collaborations with industry.

Under a CRADA with the PHS, a joint research project is specified, along with the respective intellectual contributions of the Government and collaborator. The PHS agency provides research personnel, laboratory facilities, materials, equipment, supplies, and other in-kind contributions — but not funding — to the collaborator. In general, the collaborator contributes personnel, equipment, and materials. The collaborator also may contribute funds to cover some of the added costs to the participating agency for work done under the research program of the agreement. Ultimately, the collaborator provides

the know-how needed for development and commercialization of a new product, process, or service.

A Materials CRADA has been adopted for use by the PHS. The Materials CRADA is generally used for transfers of unique research material essential in the conduct of specified research in support of the mission of the PHS laboratory. A Materials CRADA may be used if the following criteria are met: a) the material is not reasonably available from another commercial or academic source; b) the CRADA involves no other exchange of personnel or resources; and c) the CRADA has a term of not more than one (1) year.

The primary difference between CRADAs and other PHS research contracts and agreements is that CRADAs provide the commercial collaborator with an option in advance to negotiate exclusive licenses on inventions made under the research program of the agreement. Also, in carrying out the scope of work specified in the CRADA, PHS scientists are encouraged to work closely with private firms to investigate and develop technology jointly, based on the scientists' research interests.

As with other collaborative agreements, the PHS agency enters into a CRADA only when the research objective is consistent with the agency's mission. Because PHS CRADAs do not seek "sponsorship" but, rather, collaboration, CRADAs are a very cost-effective way for companies -- particularly small businesses -- to leverage their own R&D efforts.

What Is Included In The CRADA Agreement?

A typical CRADA between a PHS agency and a commercial firm includes a number of standard provisions based on policy guidelines and model agreements adopted by the PHS agencies. These include:

- Research, development, and commercialization efforts contemplated for each party.
- Contributions of the PHS agency by way of equipment, supplies, and personnel.
- Contributions of the commercial firm by way of equipment, supplies, personnel, and funding.
- Confidentiality.
- Publication of results.
- Inventions, focusing on definitions, ownership, and patent prosecution.
- Licensing.
- Liability.

What Are The Benefits Of CRADAs?

Collaboration under a CRADA results in a number of mutual benefits for PHS agencies and for commercial firms, as well as expediting public access to technology developments.

Commercial firms benefit by:

- Improved access to PHS scientists and facilities.

- Better access to expertise related to research results and inventions.
- Options to exclusive licenses on inventions made under the agreement.
- Profitable new products and processes.

PHS agencies benefit by:

- Improved opportunities to develop and transfer technology.
- Accelerated interaction with industry to transfer basic research findings to the commercial development process.
- Increased familiarity with problems related to commercialization of products and processes.
- Sharing of royalty income with individual inventors and PHS agencies.

How Can A Company Begin A PHS CRADA?

Companies can initiate the CRADA discussions by contacting a PHS scientist with whom they would like to work. Participants in CRADAs can include the individual PHS agency and one or more other parties (other agencies, state and local governments, non-profit and not-for-profit institutions, private corporations). A competitive process is generally not required in choosing a CRADA partner, although it is required by PHS fair access guidelines under limited circumstances. An agency may choose to use competition in a collaboration when interested parties are unknown or the technology/project is such that competition is in the public's best interest. An announcement may be placed in the Federal Register or Commerce Business Daily with a selection made known to the responding parties. An ad hoc evaluation committee may be formed to review submissions, if appropriate.

A written CRADA document should be developed as soon as both participating scientists negotiate the Research Plan. NIH has a model CRADA which is required and used as the basis for all negotiations with outside parties. The model CRADA contains three appendices: a) Research Plan, b) Financial and Staffing Contributions of the Parties, and c) Exceptions or Modifications to this CRADA.

PHS scientists are required to fill out and attach a Conflict of Interest and Fair Access Survey form. The purpose of this form is to assure that a PHS scientist does not have a conflict of interest regarding the CRADA research (such as consulting with the same company) and that proper consideration has been given to fair access guidelines.

CRADA Negotiation And Approval

Each PHS agency or institute has a Technology Development Coordinator (TDC) who facilitates the drafting of an acceptable CRADA and related Appendices advising the PHS scientist in the development of the overall agreement. The CRADA and Appendices are generally negotiated by the TDC in conjunction with the other party. The negotiated CRADA must be approved by the PHS scientist, the Laboratory or Branch Chief, and the Scientific Director. The TDC then forwards the agreement to the Office of Technology

Transfer (OTT) and the Office of General Counsel for review, who then forward the agreement to the CRADA Subcommittee of the Technology Transfer Policy Board for

final approval recommendation. Generally, all CRADAs containing exclusive licensing-related clauses must be reviewed by the agency's CRADA Review Subcommittee.

The FTTA provides for a 30-day period to disapprove or modify a CRADA after its finalization. When there are not changes required, the CRADA is signed and returned to the TDC at each PHS agency or institute. The TDC is responsible for obtaining the proper signatures required for execution by the company. Agreements have no mandatory term length and can be extended by the mutual agreement of the parties if there is no substantial change in the Research Plan. Because scientific objectives and circumstances change, it is essential to include in a CRADA a specific time period for financial accountability and provisions for early termination.

In order to expedite the commencement of the Research Plan, prior to final execution of the CRADA, an interim Letter of Intent may be signed with the company. Once an invention is made within the scope of a CRADA agreement, the OTT will negotiate the CRADA-related license with the commercial partner.

Session V. (continued)

QIAO Youlin: Ethical Considerations in conducting Cancer Epidemiological Studies in China.

Objective: To review the ethical standards and practices in conducting population- based cancer prevention research in China.

Background: In recent years, the increasingly biomedical research involving human participants has generated new ethical and logistical issues, Bioethics has expanded into all health professions involved in the sciences and practices of cancer epidemiology, prevention and control. Many professional groups have made ethical roles and guidelines. The profession of epidemiology is a recent example.

Recent examples include concern over the conflicts of interests, scientific integrity; the risks and benefits of chemopreventive agents to be used in randomized trials; genetic markers of cancer risk and notification, employment, and health insurance. The Chinese Guidelines on Ethical Review of Medical Research has been published by Ministry of Health in 1998.

Methods: Ethical theories commonly cited in biomedical ethics include utilitarian and deontological theories. Four principles of bioethics are beneficence, nonmaleficence, justice and respect for autonomy of persons. No quantitative approaches are involved instead of a qualitative method in this presentation.

Results: The principles of respect for persons, beneficence and justice are recognized widely in China. The protecting the rights and welfare of human research subjects are responsibilities of Chinese researchers and their institutes. A large scale (N=29,584) randomized controlled nutrition intervention trial in Linxian farmers at increased risk of esophageal cancer has been undertaken by NCI and CICAMS since 1985. Although the farmers who are enrolled in the trial may have an extraordinary risk of esophageal cancer, they will generally be asymptomatic or free of disease at the baseline, and they may not develop esophageal cancer even in the absence of any preventive intervention. Thus, healthy individuals were randomly allocated to receive either multiple vitamin/mineral supplementation or placebo over 5 years. Both IRBs of NCI/CICAMS have proved the scientific research protocol and considered it had an acceptable balance between potential risks and benefits to the trial participants. The continuing ethics reviews have been conducted by both IRBs annually for ongoing research activities. The information in the informed consent document is included description as research, constraints on experimental hazards, voluntarism in participating, scientific integrity, the safeguarding the privacy and confidentiality of research subjects and indication of placebo control. Concerning the ability of layperson (40% illiteracy) to adequately understand the potential risks and benefits associated with participation in the trial, a detailed group (community) informed consent was given by principal investigator instead of the individual will. Both signature and finger print will be acceptable for consent form. The

adequate care and compensation to participants for illness during research have been provided.

Conclusions: IRB prior review on a research proposal in ethical terms is essential. Any research protocol should minimize potential risk and maximize benefits to research subjects. Individual or group voluntary informed consent from all subjects should be obtained. Protecting privacy and equal treatment of all subject are required. The adequate health care and compensation to participants for illness during research are strong recommended.

Session V (continued)
Eric M. Meslin & James V. Lavery,
Bioethics – The Protection of Human Subjects

Before starting, we would like to make two comments. First, another colleague, Professor Judith Swazey, was going to be working with us at this forum and giving a joint presentation was not able to participate due to illness. Second, I hope this presentation is an introduction to what I hope will be much more detailed and informal discussion in the small group session.

As a preliminary remark, among the reports of the National Bioethics Advisory Commission (NBAC), one of the reports focuses specifically on the issues surrounding the use of human biological material in research. Among the conclusions that the commission came to in that report is that for perhaps the last twenty or thirty years, many of the issues in medical research and human research have tended to focus on the clinical trials paradigm, the clinical trials model. Typically this is in a hospital setting and the patient is enrolled in a study comparing one drug or another either with a placebo or with another treatment. In this context we tend to focus on the protection of the individual, the human being, the person sitting right in front of us. But in the report on biological material we have the opportunity to think about research involving human beings in which there is only material — biopsy material, blood sample, slides or data from a survey. The individual from whom the material was obtained may be many hundreds or thousands of miles away. This is one of the most important research challenges that bioethics is going to have to face.

Our presentation is divided into two parts – the first is a discussion about ethical issues as they arise in the course of conducting research, using the research process itself as a way of thinking about these ethical issues. The second part addresses opportunities for harmonization and collaboration in bioethics.

Dr. Qiao has presented us with a very nice introduction. Essentially, in the research process there are a number of areas in which ethical issues arise — in the research question itself, in the design of trials, in the recruitment of participants, in the process of disclosure and the other elements of informed consent, for example issues about confidentiality and the protection of privacy, medical data, and the whole process of the oversight of studies. This clearly is not an exhaustive list, but I would like to use it as a rough framework to talk about the distinction between process and substance in ethics. The procedural requirements of ethics focus on the processes and activities through which we try to satisfy the substantive requirement. To illustrate this I will run quickly through the main steps in the research process.

The first step in the process is the articulation of the research question. It is widely accepted that research ought to be of high quality in order to be deemed ethical. But the process of reviewing research to determine that it is sufficiently important or valuable, as well as being scientifically sound, is complex. Especially in the context of international

research, there are important issues about the relevance of any health-related research and the priority it ought to be assigned relative to other research.

In the design of trials there are challenges in identifying an appropriate sampling frame and in securing the sample itself. There is also growing concern about standard of care in international collaborative research, how research subjects are treated and what they receive through the course of a study, including the nature of the control for intervention studies. Depending on their social and economic circumstances and their general access to health care, some groups may be more vulnerable than others to consent to standards of care and treatment than would otherwise be justifiable. If researchers have little interest in the health problems facing these groups, but are focused solely on the task of meeting regulatory requirements in their home countries, these circumstances can result in research practices that are exploitive.

One of the issues that I think was highlighted yesterday, and it is a complicated issue that we are all struggling with, the recruitment of participants to trials. How are people approached? By whom? And in what context? All of these questions really go to the heart of the problems of coercion (making sure that people really are participating in trials voluntarily) and conflict of interest, for example when the physician is also the investigator. This in turn raises the issue about participants' expectations and their understanding about the nature of their participation in research. Is there a therapeutic misconception? Sometimes people will participate in studies because they believe that they are, in fact, receiving medical care through the study and do not really appreciate the full scope of their involvement or the nature of the risks they have assumed.

In terms of disclosure — the information that is given to participants as part of the consent process — Dr. Qiao has given a list of some of main requirements. In this country, these essential elements of disclosure are provided in the U.S. Federal Regulations in 45 CFR 46. The goal of disclosure is to make sure subjects are truly informed about the nature and implications of their involvement in research. In "informed consent," the "informing" part can require skill and/or caution on the part of the research team. We are trying to ensure that people have the adequate knowledge, awareness, and appreciation of the risks and potential benefits of the research they are going to take on.

I have mentioned the distinction between procedural requirements and substantive requirements of ethics. Let me give some illustrations regarding this distinction for informed consent. You will all be familiar with procedural requirements such as signed consent forms or proxy consent for incompetent subjects. Although we know that there are all kinds of ways of implementing these procedural requirements we also know that it is possible to follow all the required procedures without ever achieving the substantive goal of truly informed and voluntary consent. The overarching issue here—as Dr. Qiao identified — is respect for the person, which requires that there is a meaningful

demonstration of genuine willingness and voluntariness on the part of research subjects to allow things to be done to them that they might not ordinarily allow.

In terms of confidentiality and privacy, the process questions involve what information will be taken, where it will be taken from, who will take it, and whether or not there is a third party involved in the collection and whether the information will be stored securely. On the substantive side, trust is very significant as is protection from discrimination and stigmatization.

Finally, there is the process question of the regulation of research practices, including oversight and monitoring, that I think everyone universally finds very complicated and very difficult to carry out. Substantively, the key factor is protection of the individual, which is more easily achieved in research contexts in which there is a strong culture of protection for human subjects.

Again, it is important to get beyond the procedural requirements to really encourage and demonstrate sensitivity and concern about protection throughout the entire research process. Procedural requirements make up a large proportion of the issues and concerns that ethics review committees or IRBs routinely address and they are essential concerns. But for the substantive goals of protection to be achieved there must be a strong culture of protection and genuine concern for the rights and welfare of research subjects throughout the entire research enterprise. The process-substance distinction we make is summarized in the table at the end of this paper.

Turning to the second part of our presentation, we would like to discuss some of the initiatives that have occurred to foster international discussion on these topics. The National Bioethics Advisory Commission (NBAC) convened a global summit of national bioethics commissions to promote dialogue about ethical issues that arise in research. We have met on two occasions in Tokyo and in London. At this time, there are national commissions in 38 countries. While their responsibilities differ, these committees met to discuss a number of common bioethics subjects. In addition to the discussion occurring at the Global Summit, there have been other initiatives. As mentioned earlier, some of these issues arise in the context of the many international documents and guidelines for research involving human subjects. A number of initiatives are underway to revise and update these documents.

Within the U.S. several activities are noteworthy. There are the several initiatives carried out by NIH. There are also initiatives by the Centers for Disease Control and Prevention, the Institute of Medicine, the American Association for the Advancement of Science, and the National Science Foundation. It should be emphasized that, although you have heard much about U.S. regulations for protection of human subjects, we have not achieved complete harmonization. We have a set of regulations that are common to 17 Federal departments and agencies, but that set of regulations does not cover every situation. Nor do these regulations cover every kind of research or all private, non-governmental,

research. In other words, we have a complicated, set of regulations for our own investigators, but they these regulations are in need of revision.

Many are now observing that it is time to consider other countries and to strive to harmonize research guidelines among them. NBAC is one of many groups who have worked on this issue [NOTE: NBAC recently published a report Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries, available at www.bioethics.gov]. One of the opportunities for harmonization and collaboration is to recognize that there is no single set of international or national guidelines that have been agreed upon by every nation in the world, let alone by every investigator. While this might seem to be a very unfortunate situation, I would like to take the more optimistic view that it is an opportunity that we all have — China, the United States, and other countries — to look carefully at how research is conducted collaboratively between our countries and to find areas where there are difficulties that need to be worked through.

NBAC has, over the last year [1999-2000], been studying the topic that Dr. Keusch mentioned: the topic of international research. It was motivated by a number of considerations, one of which is a renewal of the discussion of research involving human "participants" rather than human "subjects". The word "subject" has many interpretations in English, some of which can be quite negative—for examples, that someone is subjected to the authority of others. There has been some concern that when the United States sponsors or conducts research in other countries it is contributing to the misperception that the U.S. is exploiting or otherwise "subjecting" others to research. We recognize that there is an opportunity for public dialogue and discussion where the public is very broadly defined and not just citizens of a given country, but researchers, regulators, sponsors — everyone who has an interest in the research.

The commission also was concerned about how U.S. research regulations are being "exported" to other countries. This was mentioned in the previous presentation that described the grant-making ability of the U.S. government. As a condition of awarding those grants, the U.S. can require conformity with U.S. regulations. The idea that the U.S. can make these rules may in some ways be seen as offensive, as disrespectful. But in a very practical way, it is also seen as unnecessary.

There are an increasing number of countries (China among them, from the documents we have all seen) that have research guidelines in place — guidelines that look in some ways like the U.S. regulations. So NBAC looked very carefully at how our guidelines are being interpreted in other countries. We looked at ways in which we can modify, refine, or clarify guidelines in a constructive way. The guidelines in place are 30 years old; moreover, they were not originally developed in anticipation of many new types of research going on today such as the human genome project, or the use of human biological materials; and they were certainly not prepared with the consideration of increasing scope and speed of international collaboration.

We now recognize the importance of moving towards what we hope will be a broader harmonization of these issues. Finally, there is recognition in the U.S. that it is not enough to simply export guidelines and rules. There are review committees in many countries and they sometimes lack the capacity, expertise, or experience to deal with U.S. sponsorship or problems.

In addressing now Some Possible Next Steps, I hope this will be an introduction to the small group discussion on bioethics. This area of international regulation and oversight of research is very fertile ground for discussion and cooperation. It is fertile for several reasons. First, as I mentioned, there are many international guidelines and regulations, none of which have moral authority over the whole world. Second, it is important to recognize that through most advanced communications — e-mail, Internet, CNN, and news media — we are learning more quickly about research that is occurring in other countries and we are learning about the difficulties and problems that arise. Twenty years ago, it would have taken much longer for the world to learn about the death of Jesse Gelsinger the young man that died in the gene transfer study at the University of Pennsylvania. Twenty years ago, it would have taken much longer to learn about collaborations between China and the United States.

Another reason for looking at Some Possible Next Steps is the tremendous opportunity for joint regional education. Jim Lavery referred in his presentation to the consent process. That is one example where it is not simply what should be on a piece of paper, but what is the best method of providing that information, who is the best individual to do so, how should family members, community members, and others be involved. These are important empirical questions that really call out for collaborative research where there is a joint opportunity. So Some Possible Next Steps are couched only in the most general terms (share information, seek collaborative funding for ethics issues, informing host governments) as a chance to share information on an ongoing basis. Our National Bioethics Advisory Commission is trying to do that with other advisory commissions around the world. But it is only one mechanism. The real information exchange occurs in the journals, it occurs in meetings like this.

There are tremendous opportunities for bioethics research that have not yet been explored. In one of my previous lives, I was working with Dr. Elke Jordan on a bioethics program at the National Human Genome Institute. That program was and still is one of the world's largest sponsors of bioethics research. It is to be greatly credited for taking that on. But it is only one small drop in the bucket. There needs to be other opportunities — public, philanthropic, and even private — to explore these issues. Finally, this effort cannot be effective if we only speak amongst ourselves. Interested groups that ensure engagement of government and policy makers in host countries must also be aware of these discussions and make use of them.

Our public investment in science and technology in the U.S. for Fiscal Year 1999 was $79.4 billion, of which half was used by the Department of Defense mainly for the development of weapons. I think it would be unfortunate were we in this room to have

an obsession about the remaining $40 billion in the United States and its equivalent in China. We are now at a time when science and ethics must go hand in hand. There must be equivalent research — I will not say equivalent level of funding — but there must be appropriate levels of funding for research in the areas that we have identified.

Procedural and Substantive Issues in Research Ethics

	Process	Substance
Research Question	Value Validity	relevance priority
Design	Sampling frame Sample Standard of care	vulnerability (convenience) exploitation "responsiveness to health needs"
Recruitment	How approached? By whom? In what context?	Coercion/voluntariness Conflict of interest Understanding and expectations by recruits about the research Fair distribution of risks & benefits
Disclosure	e.g. U. S. Regulatory Requirements (45 CFR 46)	Informed consent Knowledge, awareness, appreciation of risks & benefits
Consent (individual/group)	Signed form Proxy consent Consent process	Voluntariness Willingness Authorization Permission (legitimacy)
Confidentiality and Privacy	What information? From where? Processes for collection & storage and 3rd party access Promises	Trust Status of the individual Protection from discrimination, stigmatization
Regulation	Monitoring Ongoing review	Protection Culture of protection
Overall	Adequate independent review Oversight	Protection of human subjects

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