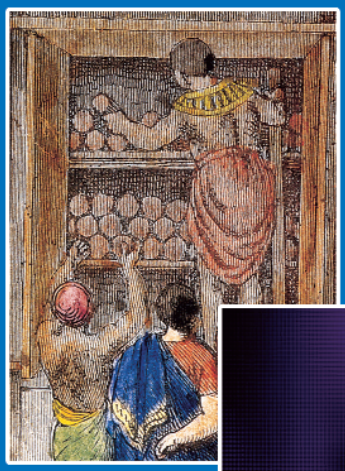

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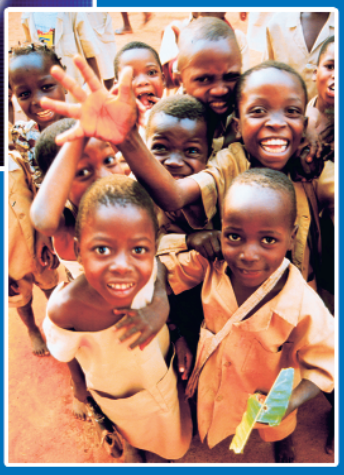

BioVision Alexandria 2004

Editors: I. Serageldin and G.J. Persley

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Discovery to Delivery

BioVision
Alexandria 2004

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Editors: Ismail Serageldin
Gabrielle J. Persley

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Preface

BioVision Alexandria and the World Life Sciences Forum, BioVision, are important gatherings of opinion leaders and prominent scientists who encourage constructive dialogue among key players in the development of life sciences. They include members of academia, industry, research, institutions, media, and society. The ultimate goal is to provide a platform of exchange and information to meet the challenges facing the 21st century in life sciences, a vital step for economic development leading to global improvement of quality of life for all.

BioVision Alexandria 2004 addressed the needs and capabilities in the new life sciences in the lesser developed nations of the world. The main goal was to promote the active exchange of ideas and innovative pathways to benefit the global community. A special section was dedicated to the issues of Ethics, Patents, and the Poor.

The overall theme of this volume is "Discovery to Delivery." This reflects the exciting new discoveries in genomics and other aspects of gene technology that are finding applications in human health care, food and agriculture, and conserving biodiversity and the environment.

However, the pathway from these exciting scientific discoveries to delivery of products to those who need them is at times a rocky road, and the pitfalls are many. Contributors to this volume have analyzed some of the constraints that hinder the delivery of new biotechnologies, with safety assurance and at affordable prices. These issues are analyzed for the sectors of food and agriculture and human healthcare, where there are some common issues, but also some differing perspectives.

An overarching concern is the need for fostering more capacity in science and technology in developing countries, so as to encourage local innovations based on mobilizing the best of global science. Centers of excellence that bring together a critical mass of people, resources, and physical facilities can play an important role in accelerating capacity building. This has proved to be the case in China and India, and is likely to be an important development in African science policy in the future.

The final word for the future invokes the tradition of the Library of Alexandria—Be Bold–Dare to Dream

Ismail Serageldin
Director
Bibliotheca Alexandrina

Gabrielle Persley
Chair
The Doyle Foundation, Scotland

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The support of the Government of Egypt in sponsoring BioVision Alexandria 2004 at the Bibliotheca Alexandrina is gratefully acknowledged. The conference was held under the auspices of H.E. Mohamed Hosni Mubarak, President of the Arab Republic of Egypt, and H.E. Mrs. Suzanne Mubarak, Chair, Board of Trustees, Bibliotheca Alexandrina. We thank H.E. Atef Ebeid, Former Prime Minister of Egypt, for his strong support and interest in the preparations for the conference and its outcomes.

We also extend our thanks to the distinguished Nobel Laureates, the Speakers, Chairs, and Rapporteurs who worked very hard, and of course the conference participants, including those at the Poster Session and the Book Fair. Above all, we thank our partners in BioVision Foundation who inspired us to go down this path in hosting BioVision in alternative years in Alexandria, Egypt and Lyon, France.

Strong support was also provided by the Arab Academy for Science and Maritime Transport (AASMT), the Egyptian Agricultural Genetic Engineering Research Institute (AGERI), the Consultative Group on International Agricultural Research (CGIAR), the International Center for Agricultural Research in the Dry Areas (ICARDA), the Food and Agricultural Organization of the United Nations (FAO), the US National Academy of Sciences, the Organization for Economic Cooperation and Development (OECD), the Third World Academy of Science (TWAS), the United Nations Educational, Scientific and Cultural Organization (UNESCO), and the World Bank. The contributions of all the sponsoring organizations are gratefully acknowledged.

We are especially grateful to Dr. Mohamed El Faham and the team who organized this conference. The contributions of the members of the national and international organizing committees for the conference helped ensure its success. The conference organizers were ably supported by the secretariat at the Bibliotheca Alexandrina, including valuable assistance on production, illustrations and information technology. Our thanks to the secretariat and to all the production staff at the Bibliotheca Alexandrina who contributed to the success of the conference and the production of this volume.

In the editing and production of this volume, Reginald MacIntyre and Ida MacIntyre undertook the technical editing of the manuscripts. Margaret Macdonald-Levy of The Doyle Foundation in Scotland assisted in preparing the final manuscripts for publication, and her skillful contributions in bringing this project to completion are acknowledged with many thanks. We are grateful to Susan MacMillan of the International Livestock Research Institute in Nairobi for making

photos available from ILRI's collection to illustrate sections of the book and the cover.

Most importantly, we thank all the contributors to this volume who converted their presentations at the Alexandria conference into thoughtful chapters for publication.

All the chapters , and their accompanying slide presentations are also available in electronic format, and may be accessed at www.bibalex.org/bioalex2004conf or via www.doylefoundation .org

We hope that the breadth of papers presented here contributes the continuing discussion as to how new discoveries in science can deliver benefits to society that are both socially acceptable and environmentally safe.

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Acronyms and Abbreviations

ACSAD	Arab Center for Studies in the Dry Areas
AFESD	Arab Fund for Economic and Social Development
AFLP	Amplified fragment length polymorphism
AGERI	Agricultural Genetic Engineering Research Institute (Egypt)
ASEAN	Association of Southeast Asian Nations
Bt	Bacillus thuringiensis
CAS	Chinese Academy of Science
CBD	Convention on Biological Diversity
CGIAR	Consultative Group on International Agricultural Research
CIBCM	Centro de Investigacion en Biologia Celular y Molecular
CLIMA	Centre for Legumes in Mediterranean Agriculture (Australia)
CPVO	Community Plant Variety Office
CWANA	Central and West Asia and North Africa
DArT	Diversity Arrays Technology
EST	Expressed sequence tags
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration (USA)
GAVI	Global Alliance on Vaccines and Immunization
GEF	Global Environment Facility (World Bank)
GIS	Geographic information systems
GMHT	Genetically modified herbicide-tolerant
GURTs	Genetic use restriction technologies
ICARDA	International Center for Agricultural Research in the Dry Areas
ICGEB	International Centre for Genetic Engineering and Biotechnology
ICSU	International Council for Science
ICT	Information Communication Technologies
IFAD	International Fund for Agricultural Development
IFPRI	International Food Policy Research Institute
IPGRI	International Plant Genetic Resources Institute
IPR	Intellectual property rights
IRRI	International Rice Research Institute
MAS	Marker-assisted selection
MHLW	Ministry of Health, Labor and Welfare (Japan)
MTA	Material transfer agreement
NARS	National agricultural research systems
NGO	Nongovernmental organization

NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OECD	Organisation of Economic Cooperation and Development
PBR	Plant breeders' rights
PCR	Polymerase chain reaction
PCT	Patent Cooperation Treaty
PVP	Plant and variety protection (certificates)
QTL	Quantitative trait loci
RFLP	Random fragment length polymorphism
RRA	Rapid rural appraisal
SARS	Severe acute respiratory syndrome
SNP	Single nucleotide polymorphism
SSP	Seed storage protein
SSR	Simple sequence repeat (microsatellites)
TIGR	Institute for Genome Research (Germany)
TILLING	Targeting Induced Local Lesions In Genomes
TRIPs	Trade-Related Aspects of Intellectual Property Rights
TWAS	Third World Academy of Sciences
UNCCD	United National Convention to Combat Desertification
UNDP	United Nations Development Programme
UNESCO	United Nations Educational, Scientific, and Cultural Organization
UNFCCC	United Nations Framework Convention on Climate Change
UNICEF	United Nations Children's Fund
UNIDO	United Nations Industrial Development Organisation
UPOV	International Union for the Protection of New Varieties of Plants
WANA	West Asia and North Africa
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WIPO	World Intellectual Property Organization

Foreword

H.E. Atef Ebeid

Former Prime Minister
Arab Republic of Egypt

On behalf of the Egyptian Government I welcome you to our country, and wish you a pleasant stay and a successful conference. I wish to thank the organizers, especially Ismail Serageldin, as well as the distinguished participants for selecting the right topic, at the right place, and at the right time. Global cooperation is needed to help meet the key challenges facing humanity: Poverty and the availability of affordable medical care. Our hope lies in the contributions made by scientists, the response of entrepreneurs, and the commitment of governments.

The papers prepared for this conference, including the assessment of the Egyptian experience, clearly show remarkable progress in the last 50 years. We have learned five important lessons from the presentations, in my view, and I share these with you for further debate.

First, we learn that technology to enhance agricultural production should be given special attention, and highest priority. Egypt, through the scientists working in agriculture, was able to foster and achieve fast, equitable, and sustainable growth. The yield of the five basic crops became the highest in the world in less than 15 years.

A second lesson is that the strategy for poverty reduction should address improving the productivity of poor people's own assets. We must direct special attention to those who farm limited areas and own few resources. As well, safe, effective vaccinations should reach every child and every home.

The third lesson is that limited national financial resources should not discourage developing countries from embarking on a national program of technological transfers. Egypt started its program at a time when annual per capita income was less than US$1000, and it was fairly rewarded.

The fourth lesson is that with limited research resources available, we should resist the temptation and the pressure to operate too many programs. A few effective ones are much more rewarding than many under-funded ones.

The final lesson is that partnerships with international counterparts from industrial countries are strongly recommended. Such alliances save time and money, and provide opportunities for training. The hosting of international research centers has been and will continue to be welcomed in this country.

There are important challenges ahead for scientists and governments, with

biosafety being one of the most important. Enforcement of biosafety regulations must be pursued vigorously. Our experience is limited, and needs to be enriched in areas of regulation, capacity building, and coordination among supervisory agencies. Egypt needs technical assistance as well as additional opportunities for training. Linkages with responsible agencies and other countries will help us gain the necessary experience.

A second important challenge is establishing partnerships between universities, research centers, farmers and industry. Despite the availability of funds, each party is waiting for the other to make the first step. Our people now recognize the value of joint ventures, and we encourage more of these. Experience in other countries has been successful and rewarding, and we should learn from them.

Another future challenge is managing national programs for the transfer of biotechnology. Success will depend on availability, ability, accountability, and acceptability. The availability problems are related to the existence of satisfactory intellectual property rights, supported by effective enforcement mechanisms. We also need to expand our knowledge of sourcing, selecting, negotiating, and contracting.

Our abilities need to be enhanced in areas such as building local capacities for receiving, experimenting, assessing, and training. Improved public awareness must not be neglected, to ensure transparency and public support. A clever decision-maker knows very well that resources are scarce, and ensures accountability by setting priorities based on reliable cost/benefit analyses, and determining the expected time for the recovery of investment.

Acceptability simply means that the society at large, as well as the potential users, should be convinced and willing to use the new technologies. This needs effective presentation of the experiences of other countries, as well as locally successful experiments. The most important challenge is the country's success in widening and deepening international cooperation. All options have to be open: buying, leasing, joint-venturing, co-funding, licensing, auditing experiments, and direct marketing.

What really counts is the contribution to the welfare of society. The challenges for developing countries are many. At the top is the supply of adequate food and medicine. Only science and its applications can meet these challenges. The government will work harder, and we will search for more ways to provide needed facilities, and protection for intellectual property. We care about our scientists, and we share your hopes for a better.

Foreword

Ibrahim Badran
Former Minister of Health, Egypt

The so-called hard sciences have exceeded the pace of the soft sciences by many years. Take, for example, the science of ethics and the ethics of science. Other related fields were forgotten for decades and were revived only after World War II. World medical associations became concerned after the Helsinki Declaration in the 1940s, and the World Health Organization showed its deep concern only recently.

The great economist Shoemacher stated in his book, "Small is Beautiful," that life is too precious to be left to scientists, engineers, and economists. In his thesis he stressed that, if life was left to them alone, the morality of ethics would have disappeared soon after the industrial revolution.

It is true that science and technology are very beneficial to humans, but also create enormous risks when used to create nuclear bombs, guided missiles, and biological and chemical weapons. The creative geniuses who invented some of these products later regretted their efforts.

The science of ethics and bioethics can be called the disciplined study of morality, human reactions, and deeds. These are heavily influenced by deeply rooted cultures, ever-expanding knowledge, and above all, the influence of spirituality.

Throughout history, science was based on knowledge, attitude and practice, which were interwoven in a matrix of morality and fundamental ethics. This in turn governs all relations between people and nations, through a group of laws and principles that maintain life. Federico Mayor in his thesis on "Ethics of Life" said the role of physiology, the science of life, must be carved out of its relationships, to be changed from the genome and molecular biology to the modern evolutionary biology and its relation to ethics and the environment.

A capacity building system for ethics should be developed so that a group of specialized trained ethicists is available as a critical mass of experts to guard against science that could be disastrous to all forms of life, including humans. This would form a protective barrier against human error and unwanted aggression.

Foreword

Philippe Desmarescaux

Chairman
The World Life Sciences Forum, BioVision, France

I am especially pleased to witness the steady development of BioVision Alexandria, with a challenging program, speakers, and participants of great quality.

When we launched the World Life Sciences Forum initiative in 1998, with the former Prime Minister Mr. Raymond Barre and the Permanent Secretary of the Academy of Science Professor Francois Gros, we sensed that the concept would grow and expand. We also felt that BioVision would become global and encompass as a matter of priority the North-South and South-South issues.

The results carried out in Alexandria, thanks to the steady involvement of our Vice Chairman Professor Ismail Serageldin and his team, give us great pride and hope for the further development of this essential platform.

Life Sciences is clearly the fastest and most challenging path toward shaping the 21st Century, to the benefit of all stakeholders. This development will only occur, however, for the benefit of industrial and developing countries under the following conditions:

- Dialogue is of the essence: A proper public perception leading to the shared understanding of threats and opportunities is essential. Progress cannot be forced upon society at large, and a continuous flow of objective information around key issues is the only way forward.
- Bioethics should be enhanced at all stages to facilitate the acceptance of fascinating new fields of activity.
- Concrete actions should be given top priority, especially with regard to North-South relationships. An adapted regulatory environment, along with a real involvement of the pharmaceutical and agri-food industries must lead to solid partnerships. Foundations such as ours exist to catalyze and cement these priorities, with a growing understanding that progress not equally shared is a step backward.

BioVision is hoping to help put Science, Society, and Industry on equal footing. We count on the active participation of BioVision Alexandria to start building a network leading to concrete actions. It is our collective duty to reduce disagreement, define priorities, and emphasize precautions to be taken. Diversity of opinions and

cross-breeding of ideas will lead to unexpected opportunities, again to the benefit of both developing and industrial nations.

We not only have the moral obligation to prepare for the future, but we have the duty to avoid errors, by helping to ensure wealth and health in a secure environment.

The industry leaders need to realize that the developing countries are also potential partners with surprising opportunities. The scientists need to recognize that there is a clear continuum between the young PhD and Nobel Laureate: wisdom and change are of the essence, regardless of age and geography. And, last but not least, civil society representatives need to understand that a global vision is essential, and that slowing down innovation could have damaging consequences.

Foreword

Massimo Garzelli
Head of Regional Office, UNIDO, Egypt

A Global Biotechnology Forum jointly organized by UNIDO and the Government of Chile was held at Conception (Chile) in March 2004. The objective of the forum was to examine the potential offered by biotechnology in its various forms, in particular the creation of wealth and improvement of the quality of life of people in developing countries and countries with economies in transition.

Underlying this broad objective were a number of specific goals:

- To examine biotechnological opportunities and challenges in developing countries.
- To examine possible restrictions and policy issues in relation to such opportunities and challenges, and suggest mechanisms to overcome such situations.
- To explore means of capacity building, particularly in scientific and business skills.
- To explore potential for contributions to health care and pharmaceuticals from biotechnology in developing countries, relating both to internal use and potential export markets.
- To explore mechanisms of technology transfer.

This list is not exclusive, but it illustrates the kind of objectives and issues considered and brought forward for discussion during the forum.

UNIDO has played a catalytic role in the promotion of biotechnology in developing countries, through the establishment of the International Centre for Genetic Engineering and Biotechnology (ICGEB) at Trieste, Italy, in 1985.

UNIDO's specific contribution will be restricted to its mandate, and in particular to the field of industrial biotechnology and its potential applications for raising productivity, effective environmental management, and enhancing sustainable livelihoods for poverty alleviation. Agenda 21 conferred an explicit mandate on UNIDO in regard to the environmentally sound management of biotechnology.

Operationally, the Chile Forum was structured in two parts; the first consisted of four regional consultation meetings covering biotechnology in Africa (March 2003), Latin America and the Caribbean (July 2003), Europe (December 2003), and Asia and the Pacific (December 2003). The regional meetings provided a backdrop of information on the current status and level of development of biotechnology in the industrial and developing countries, as well as potential insights for the future. These

meetings provided the platform for the Chile Forum, with a comprehensive program of presentations by leading scientists, industrialists, and policymakers.

Some of the points raised in the Final Statement, issued at the end of the 2004 Global Biotechnology Forum, included: the overall objective of the Global Biotechnology Forum was to examine the potential offered by biotechnology in all its aspects, for the creation of wealth and the improvement of the quality of life of people in the developing countries and countries with economies in transition.

The participants examined a broad range of issues related to this objective through structured dialogue on:

- Biotechnology meeting the needs of the poor.
- Biotechnology, biodiversity, energy, and the environment.
- Trade, regulation, biosafety, and social acceptance of biotechnology.
- Biotechnology and bioindustry.
- Biotechnology and developing countries.

The participants emphasized the importance of nations increasing their efforts to achieve the UN Millennium Development Goals, and they also took note of the provisions of the Monterrey Consensus. They noted that the World Food Summit of June 2002 urged research institutions and United Nations organizations to advance agricultural and other areas of research into new technologies, including biotechnology. They also concluded that the introduction of such new tried and tested technologies should be accomplished in a safe manner, within appropriate regulatory frameworks, and adapted to local conditions to help improve agricultural productivity in developing countries. They also noted that the World Summit on Sustainable Development in 2002 recognized the need to provide additional financial and technical resources to developing countries, to promote practicable measures to capitalize on benefits arising from biotechnology.

Participants took note of the United Nations General Assembly resolution 58/200 of 23 December 2003, which reaffirmed the vital role of new technologies in raising the productivity and competitiveness of nations, and the need, inter alia, for capacity building measures promoting the transfer and diffusion of technologies to developing countries and countries with economies in transition. In addition, this resolution took note of the proposal of the Secretary General for an integrated framework for biotechnology development within the United Nations system, and the need for strengthening coordination between relevant organizations and bodies of the system in biotechnology. Participants suggested that the following initiatives and proposals could be further considered and followed up by United Nations organizations (based on their respective mandates and approval by their governing bodies), other international development partners, the scientific community, and the private sector:

- Formation of a multi-stakeholder forum, involving United Nations specialized agencies and other international bodies together with representatives of

government, industry and the scientific community to serve as an ongoing platform for informed dialogue on biotechnology and the way in which its benefits may be used for the enhancement of developing countries.

- Creation of an information network and database on what biotechnology activities are currently in progress in the countries with economies in transition and developing countries, together with market information on a global basis, to assess technology and market potentials for new initiatives, including partnerships.
- Enhancement of efforts for the mobilization of resources for capacity building.
- Examination of the impact of, and ways to facilitate access to, intellectual property to promote the exploitation and dissemination of biotechnology in developing countries.

The Forum provided valuable inputs into the United Nations-wide effort to spread the benefits of biotechnology to developing countries. It will contribute toward the Secretary General's system-wide integrated framework for biotechnology development. UNIDO presented the results and recommendations of the Forum to its Industrial Development Board in May 2004, for discussion and endorsement.

Foreword

François Gros

Honorary Permanent Secretary
Academy of Sciences, France

In connection with the BioVision Alexandria Forum, the Aventis Pasteur Foundation recently decided to create a new prize. The Foundation wishes to encourage and stimulate research activities related to solving disease problems in developing countries. The Jury of the Foundation, or the scientific committee of the organization, is headed by Philippe Kourilsky, who is now the president of Aventis Pasteur. The Jury decided to award this Prize in 2004 to a young talented microbiologist, Armelle Phalipon.

As a former director general of the Aventis Pasteur Institute, it is a privilege to offer my congratulations to this extremely talented scientist. Armelle Phalipon received a PhD in 1998 for work on DNA.

But let us move to a very important subject, which is the attempt to explain on a molecular basis the phenomenon of virulence of bacteria. Armelle Phalipon specialized in molecular genetics, and in the fight against infectious diseases. This was done in the department headed by Professor Philippe Sonsoncity, who is a member of our Academy of Sciences in France, and who is of course well known for his investigation in the field. Their work was directed against infectious diseases, but more particularly the mechanism of virulence of a particular group of bacteria, dangerous pathogens endemic in developing countries, namely Shigella. Shigella, contrary to most bacterial pathogens, is a type of bacteria that is used to penetrate the cells of the infected host. They can invade the intestinal mucosa, and they can also penetrate the epithelium cell itself. They propagate from cell to cell, liberate some toxins causing acute dysentery, and some of the Shigella species are indeed extremely harmful because they can sometimes cause fatal diseases that are particularly prevalent in developing countries.

More recently, Phalipon has attempted to determine the mechanism of the immune response against the types of dangerous bacteria that can lie hidden inside the cell. She is trying to show that there are different types of immune defense mechanisms that are directed against the bacteria before they penetrate the cell, and another that is mediated by immunoglobulin molecules that attack the infection after penetrating the cell. This work follows a tradition set many years ago by Louis Pasteur, which is a typical example of his basic study on bacteria that can lead to concrete ways to address and eventually solve some of the health problems in developing countries.

Foreword

Mohamed H.A. Hassan

Executive Director
Third World Academy of Sciences (TWAS)

The “cyber-library,” so staunchly supported by Ismail Serageldin, promises to turn millions of books, speeches, video clips, and three-dimensional images of archaeological artifacts into an electronic archive. It will be accessible on computer screens via the Internet in Egypt and throughout the world. The Alexandria Library project is a noble initiative, and one that is well worth our support and attention.

The Third World Academy of Sciences is striving to be more than an institution that functions solely for the benefit of its members. We have established regional offices, including one at the Bibliotheca Alexandrina, to bring the Academy into closer contact with regional issues. We have elected renowned economists and social and political scientists as TWAS members to enable the Academy to better address critical science-related issues of importance to society. We have published reports on fundamental problems in the developing world that include action-oriented strategic solutions to these problems. We have established a series of institutional networks focusing on fundamental environmental and social problems in the South. Through these initiatives we hope to help address issues that are of critical importance to the people of the developing world.

Frontier research in the basic sciences is now largely dominated by the biological sciences. As a reflection of this trend, the Third World Academy of Sciences now awards 60 percent of its 50 yearly research grants to researchers working in the biological or medical sciences. This program, which provides support to young scientists in the least developed countries on the basis of merit, makes the Academy a significant force in the development of life sciences capacity in the South.

The Academy stands ready to explore with others–individual scientists and scientific institutions–the broad-based issues being addressed at this conference. With our experience and wide-ranging network of contacts, we believe the Academy can make useful contributions.

When a student recently asked Nobel Laureate Sydney Brenner, one of the world's foremost life scientists, what ethical standards should be adopted by his colleagues, he had this answer: “Tell the truth and stand up for humanity.”

This simple set of principles should guide all of our efforts as we seek to explore–and embrace–the new life sciences: the most compelling science of our

times and one that holds great promise in public health, food production, and environmental protection.

The pursuit of this science does raise compelling social and ethical issues that cannot be ignored. If, as Brenner suggests, truth and compassion guide our discussions, I am sure that we can devise strategies for putting new scientific and technological findings in the life sciences to work in ways that benefit all people.

Foreword

Koji Omi

Member of the Japanese House of Representatives and
Former Minister of State for Science and Technology Policy Japan

The new century is widely considered to be the century of life science, as we move into the post-genome era.

Our resources must now be concentrated in fields where Japan has advantages in technology. We want to contribute in the most effective way, on an international level, to solving the problems confronting humankind. Japan's policy emphasizes research into a genome network, analysis of single nucleotide polymorphisms (SNP), and analysis of the structures and functions of glycogenes and sugar chains.

We have launched a genome network research project, to understand the mechanisms by which the complete set of genes encoded in the human genome develop various functions. We are also establishing Biobank Japan, consisting of DNA and sera from 300,000 patients, and are extensively analyzing SNPs to isolate genes of medical importance. This research will allow us to develop novel drugs, as well as to establish "personalized medicine" that permits individualized treatment, and helps us to avoid adverse drug reactions.

In recent years, we have experienced outbreaks of avian influenza, as well as SARS, both of which occurred in Asia. Zoonotic infectious diseases are a common concern for the international community. Japan will cooperate with the international community to solve these problems.

New types of therapies using embryonic stem cells and cloning techniques are considered a promising area of research. However, we must deal with the bioethics issues. It is important that common international standards be established. I look forward to the creation of an international consensus on life science and ethical issues.

The explosive progress of science and technology in the past century has brought prosperity and enriched the quality of life for humankind. However, the advance of science and technology raises important ethical, safety, and environmental issues. These issues are beyond the control of any single country, and also of the scientific community alone, because many problems will need to be resolved through the revision of social systems, international collaboration, and the development of common rules.

BioVision Alexandria has brought together people from developing and industrial nations to discuss many of these issues, and I hope we can contribute to human progress through future biotechnology initiatives.

Foreword

Mamphela Ramphele

Managing Director, Human Development Network
The World Bank, Washington, D.C., USA

I have drawn a special feeling of connection to the great tradition of learning that first flourished in Alexandria millennia ago, and continues today. I am proud to survey the future of the life sciences from this vantage point, and engage such distinguished colleagues over what we will make of the incredible opportunities arising from progress in the biological sciences. I am also especially satisfied to feel that this city, this country, and this continent, which is my continent, will draw on the strength of its tradition to launch into the 21st century with the highest aspirations for intellectual achievement and intellectual leadership.

We have come together at a time when half of the world's population lives in poverty, and more than one billion people are in extreme poverty (defined as living on US$2/day and US$1/day). We are conscious that over 800 million people remain food insecure. This conference takes place against the backdrop of a world in which the international community has pledged itself to meet the Millennium Development Goals by 2015. Most importantly, perhaps, the conference acknowledges that the impact of science on poverty will be a result of the forethought we have and the efforts we make to ensure its meaningful incorporation into policy decisions.

While we acknowledge the global trend toward rising incomes, and the positive impact this will have in the developing world, we know that economic growth alone is not the answer. Especially in areas where science has the greatest impact–health, food security, and environmental sustainability, the increased incomes that are predicted in the developing world will not by themselves be sufficient to allow countries to meet their MDG targets for such things as child mortality or reversing the spread of HIV/AIDS. This conference has endorsed the ethical responsibility of the science community to look forward and act in ways that bring the benefits of our expanding knowledge to the world's poor people.

We already have too many examples of technological marvels that are, at best, ethically neutral. We need more innovations that not only show our mastery of nature through knowledge, but affirm our concern for human rights and dignity. And let us not settle for progress that increases comfort for one segment of humanity unless we also see progress that increases hope for all.

In choosing to entitle this gathering "BioVision Alexandria" our hosts have given equal emphasis to the contribution of the life sciences and the vision we have

of the difference they can make through social applications.

In considering the likely impact of the biosciences for the future, I would propose that the first questions we need to ask in analyzing the impact of "the new biology" are: how well do the social sciences serve as a bridge between advances in the biology and policy? And what complementary knowledge and skills will allow scientific knowledge to appropriately guide social policy?

As the advanced state of our current knowledge in the life sciences creates more technical solutions for the problems of poverty, it drives us toward more elusive questions in the domain of social and information scientists. For example, the science behind oral rehydration is clearly understood. The challenge now is to understand the factors that influence its use and the ways policy can increase successful outcomes. Much is known about the biological aspects of HIV/AIDS transmission, but how well do we understand the issues of powerlessness and exclusion of women that seem to be the critical determinant of new infections? As genetically modified organisms increase the potential for new systems of micronutrient delivery, what will determine who takes advantage of these and why?

The World Bank is fond of saying that progress against poverty is greatest in countries that have "good policies." Leaving the tautological aspects of this remark aside, what I believe my economist colleagues mean to express by this statement is that progress against poverty is greatest where policymaking is pragmatic and evidence-based, and where it is informed by reliable data and information. Put another way, policies are most effective when social science has become a bridge between experience and legislation. Politics is a messy business, but a culture of social science creates ground for political discussion in a way that greatly increases the chances of successful policy outcomes. Our technological optimism should be tempered by the realization that effective policy formulation calls for a critical mass of expertise in the social and information sciences as well as natural science. Moreover, as important as global expertise is, nothing is more powerful for local problems than local expertise with a global perspective.

Section 1

Nobel Laureates: Perceptions and Insights

Chapter 1

Introduction to Nobel Laureates at Biovision Alexandria 2004

Ismail Serageldin

The four Nobel Laureates who shared their perceptions and insights at BioVisionAlexandria 2004 helped provide a seamless blend of science to understand the dilemmas facing science and society. It is my pleasure to introduce to you the following distinguished scientists:

- Professor Ahmed Zewail (Egypt), 1999 Nobel Laureate in Chemistry.
- Professor Jean-Marie Lehnb (France), 1987 Nobel Laureate in Chemistry.
- Professor Ryoji Noyori (Japan), 2001 Nobel Laureate in Chemistry.
- Professor F. Sherwood Rowland (USA), 1995 Nobel Laureate in Chemistry.

A common theme of all four Nobel Laureates is the more we know, the less we understand. Future challenges require a multidisciplinary approach where branches of science are merging together. However, the three pillars of science remain: *Basic research, Technology development, and Society values*, with Basic research the foundation of knowledge.

How can we harness this global community that believes in common humanity, and is determined to pursue a greater understanding of the processes of life that constitutes the new life sciences of this century?

An even greater understanding of the processes of life and means of acquiring knowledge is required to bring closer to reality the promise that is implicit to science: *It will indeed one day be able to heal the sick, protect the environment, feed the hungry, and bring dignity to work.*

Science can and has the promise to do all this, but perhaps institutions and structures in which we work are preventing the best of science from serving humanity.

The distinguished Nobel Laureates who attended Biovision Alexandria 2004, were invited to present talks that would reflect their scientific interests but that would also look at areas of research that go beyond the generally accepted limits of the life sciences. Their presentations challenged the audience to seek new ways of looking at the world, the world of science, and the future of humankind.

1999 Nobel, Ahmed Zewail

"…We need to understand the physics, the mathematics and the chemistry of biology, to make improvements in life sciences…" ***Ahmed Zewail***

Professor Ahmed H. Zewail, born in Egypt in 1946, won the 1999 Nobel Prize in Chemistry for his groundbreaking work in "showing that it is possible with rapid laser techniques to see how atoms in a molecule move during a chemical reaction."

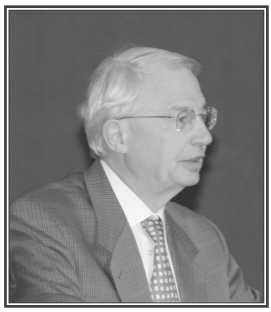
Professor Zewail is Linus Pauling Professor of Chemical Physics, and Professor of Physics at the California Institute of Technology (CalTech), and Director of the NSF Laboratory for Molecular Sciences. He is internationally recognized for his efforts in a field that he pioneered, femtochemistry. This technique uses ultra-fast lasers to probe chemical reactions as they actually occur in real time.

Because reactions can take place in a millionth of a billionth of a second, Zewail's research has, with state-of-the-art lasers, made it possible to observe and study this motion for the first time, thus allowing scientists to explore nature at its fundamental level.

Specifically, Zewail seeks to better understand the way that chemical bonds form and break. With the development of laser techniques, he and his team have been able to obtain greater insights about the exact nature of chemical bonds. The finding has had wide-ranging impact on chemistry and photobiology worldwide. Zewail's current research is devoted to dynamic chemistry and biology, with a focus on the physics of elementary processes in complex systems.

Professor Zewail's other honors include the Robert A. Welch Prize, the King Faisal Prize, and the Peter Debye Award. From Egypt, he received the Order of the Grand Collar of the Nile, the highest state honor; and postage stamps were issued to pay tribute to his contributions to science and humanity.

Professor Zewail's paper is entitled: "Time's Mysteries and Miracles: Consonance with Physical and Life Sciences"



1987 Nobel, Jean-Marie Lehn

"…There is no biology without chemistry and chemistry is the science of informed matter. On the molecular level, it represents storage while on the supra-molecular level it represents processing…" ***Jean-Marie Lehn***

Jean-Marie Lehn is a French chemist, born in 1939, who received his PhD from the University of Strasbourg in 1963. A Professor at Louis Pasteur University (1970-78) and since 1979 at the Collège de France, Lehn did groundbreaking research in the creation of artificial enzymes.

Lehn expanded on the work of Charles J. Pedersen in synthesizing crown ethers, a class of two-dimensional, ring-shaped organic compounds that are capable of selectively recognizing and combining with other molecules. In the course of his efforts to synthesize three-dimensional molecules that would possess similar reactive characteristics, Lehn created a molecule that combines with the important neurotransmitter, acetylcholine, in the brain. This raised the possibility of creating artificial enzymes that function better than the natural enzymes found in the human body.

Lehn shared the 1987 Nobel Prize in Chemistry with Pedersen and Donald J. Cram for the development and application of molecules with highly selective, structure-specific interactions, that is molecules that can "recognize" each other and choose other molecules with which they will form complexes.

This work laid the foundation for the active interdisciplinary area of research within chemistry that has now come to be termed host-guest chemistry or supra-molecular chemistry.

Professor Lehn's paper is entitled: *"Supra-molecular Chemistry: Some Contributions to Life Sciences"*

2001 Nobel, Ryoji Noyori

"…Producing and designing drugs implies the mastering of a full range of key structural characteristics. Elementary composition, atom connectivity, configuration, and conformation are the basis of molecular properties and functions…" ***Ryoji Noyori***

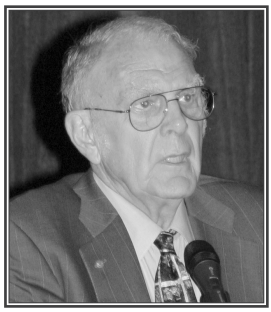
Ryoji Noyori, born in Japan in 1938, shared half of the 2001 Nobel Prize in Chemistry with William S. Knowles "for their work on chirally catalyzed hydrogenation reactions." The other half went to K. Barry Sharpless.

Noyori and Knowles developed molecules that can catalyze important reactions so that only one of the two mirror image forms is produced. The catalyst molecule, which is chiral itself, speeds up the reaction without being consumed, and just one of these molecules can produce millions of molecules of the desired mirror image form. Their work opened up a completely new field of research in which it is possible to synthesize molecules and materials with new properties.

The results of their basic research are being used in industrial syntheses of many pharmaceutical products such as antibiotics, anti-inflammatory drugs, and heart medication.

Noyori has been a Professor of Chemistry at Nagoya University since 1972, and is currently the President of RIKEN (the Institute of Physical and Chemical Research), Japan's top center of excellence in the field of natural science and technology. In addition, he is a member of the editorial boards of more than 30 international journals, and has served as Science Advisor for the Japanese Ministry of Education, Culture, Sports, Science and Technology.

Professor Noyori's paper is entitled: *"Asymmetric Catalysis: Roles in Biomedical Science and Technology"*



1995 Nobel, F. Sherwood Rowland

"…this natural bridge which lies between scientists from different countries offers optimism for the 21st century, the ability to make your decisions on the basis of actually how nature operates rather than whatever position you held when you went into it and speaking for the academies of the world, the Library of Alexandria can be a beacon for all of us…" ***Sherwood Rowland***

Sherwood Rowland, born in 1927, is an American chemist who shared the 1995 Nobel Prize in Chemistry with chemists Mario Molina and Paul Crutzen for research on the depletion of the Earth's ozone layer. Rowland specializes in the research areas of radiochemistry, photochemistry, and atmospheric chemistry. Rowland, while working with Molina, discovered that manufactured chloroflurocarbon (CFC) propellants accelerate the decomposition of the ozonosphere, which protects the Earth from biologically harmful ultraviolet radiation.

Rowland and Molina theorized that CFC gases combine with solar radiation and decompose in the stratosphere, releasing atoms of chlorine and chlorine monoxide that are able to destroy large numbers of ozone molecules. Their research initiated a federal investigation of the problem. Research on CFCs and stratospheric ozone eventually led, in the 1970s, to the regulation of use and manufacture of CFC-based aerosols in the United States, Canada, and Scandinavia. The discovery of the so-called hole in the ozone layer over Antarctica in the mid 1980s supported their theory further. In 1987, the Montreal Protocol of the United Nations Environment Programme became the first international agreement to control and reduce atmospheric damage by banning CFC production after 1996. Measurements of CFCs in the lower atmosphere confirm that the global response to this protocol has been remarkable.

Rowland has also been investigating the effect of methane gas, which has been steadily increasing in concentration, on the atmosphere. Methane absorbs global infrared radiation, and increases in its concentration contribute to the "greenhouse effect," the gradual warming of the earth's surface.

Rowland is currently the elected Foreign Secretary of the National Academy of Sciences. Prizes received by Rowland include the Tyler World Prize in Ecology and Energy and the Albert Einstein Prize.

Professor Rowland's paper is entitled: *"The Changing Atmosphere in 2004"*

Chapter 2

Time's Mysteries and Miracles*: Consonance with Physical and Life Sciences

Ahmed Zewail

Introduction

Ever since the dawn of history, humans have been the benefactors of time's miracles, but at the same time they have been baffled by time's mysteries. More than six millennia ago, the philosophy and measurement of time occupied the minds of scholars in the land of Bibliotheca Alexandrina, and, even today we struggle with the meaning of time. In this overview, I present some concepts and techniques developed in the science and technology of time, and an exposé of some of the mysteries and miracles that are in harmony with physical and life sciences.

Einstein spent a great deal of time thinking about time. In his theory of relativity, time is relative; its passage depends on how fast we travel relative to the speed at which light travels (300,000 km per second). In principle, time can be dilated and even stopped. Shakespeare knew this when he said "And time that takes survey of all the world must have a stop."

Perhaps the most puzzling issues, which have been with mankind for millennia, can be expressed in three questions: What is time? Why does it have a direction? How can it be resolved? The most complex question of all is the first one, because we really do not know what time is, and this leaves us with gray areas in the science and philosophy of time. One definition was given by C.J. Overbeck: "*Time is the great gift of nature which keeps everything from happening at once.*" Independent of its definition, we know that our perception of time depends on its duration, scale, and universality.

*Based on the Albert Einstein public lecture delivered in New Delhi, and adapted for the BioVision Nobel Laureates Day.

From the Microscopic to the Cosmic

All phenomena that we know of in our universe are defined by their time scales. Enduring or ephemeral in their character, these phenomena seem to follow an intriguing logarithmic scale of time that spans the very small (microscopic) world and the very big (cosmic) world. The human time-scale lies almost in between, a geometric average of the two extremes (Figure 2.1). The time of the big bang, the age of the universe, is about 12 billion years, or tens of 10^{+15} second (+15 on the log scale), recalling that one year is 32 million seconds. For the lightest atom, hydrogen, the time scale for the motion of an electron in its first orbit is about a tenth of a femtosecond, or a tenth of 10^{-15} second (-15 on the log scale). The average of the two limits is on the scale of seconds (zero on the log scale), the human heart beat–something to think about!

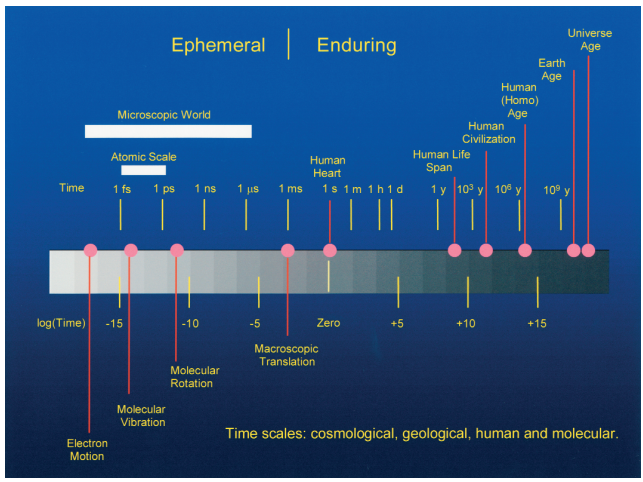


Figure 2.1. Time scales in cosmological, geological, human and molecular events.

On this log scale, we did not consider the ultimate–shortest–time of the universe, what is now known as Planck's time. In his attempt to give a universality to constants of nature, Planck in 1899 proposed that natural units of mass, length, time, and temperature can be constructed from the most fundamental constants: the gravitation constant G, the speed of light c, and the constant of action h (which now bears his name). By dimensional analysis, the shortest possible time becomes:

$$t(Planck) = (h\,G/c^5)^{1/2}$$

which is 10^{-43} seconds, and the corresponding length is 10^{-33} cm, obtained simply by multiplying by c. Even before 1900, the year quantum mechanics began to emerge, this unity in defining Planck's time is telling of "relationships" between quantum

mechanics (*h*), gravity (*G*), and relativity (*c*). Implicit in this unification is the meaning of physical laws at scales below these values, and the nature spacetime with a universal speed of light – Einstein enters here!

Time, Light, and Relativity

Before Einstein, the great contribution by James Clerk Maxwell gave us a universal description of the nature of light. By a unification of electricity and magnetism, light, as a wave, propagates in space and time with electric and magnetic (electromagnetic) disturbances. This was a brilliant contribution expressed quantitatively in Maxwell's equations. Einstein in 1905 was concerned about two issues that relate to the nature of light–Is it really a wave? and, What happens to these waves if you can imagine running with them near the speed *c*? The first issue is not our concern here, but the second one is.

Something is special. Whichever direction a beam of light is coming from, independent of our own velocity for observation on Earth, we will always measure *c* for light. Einstein, in his special theory of relativity, gave the correct picture for adding velocities: For a motion of an object (say a moving ball) with velocity v in a reference frame (say a moving train) with a velocity *u*, an observer will see a motion not by the expected v + *u* velocity, but by v + *u* divided by the factor $(1+vu/c^2)$; when the speeds v and *u* are the "normal" ones, that is, much less than c, then the total velocity is the expected (Newtonian) v + *u.* However, if instead of the ball we have light with speed *c*, then the total velocity becomes *c* + *u* divided by $(1 + u/c)$ which is exactly *c*. The speed of light is the same in all reference frames, in all directions, for all observers, and every observer will experience the same natural laws.

The consequences of these findings for time, length, and mass require some philosophical interpretation. As the speed of light is approached, the length of a spaceship will shrink and approach zero in the direction of the motion. Similarly, moving objects become more massive and approach infinity when the object velocity becomes near the speed of light. For time, the mystery continues. Moving clocks must slow down and stop when the object velocity reaches the speed of light. In this "Dilation of Time," time becomes relative:

$$t(\text{moving}) = t(\text{stationary}) \,/\, (1\text{-}v^2/c^2)^{1/2}$$

where the velocity of the moving clock is v. From the expression, we note that the time of the moving clock gets longer (slowing down) as v increases, but we also note that if v is made to exceed *c*, we enter an imaginary world of time! Thus, within the framework of this theory, the speed of light is the ultimate speed in our world and universe.

In approaching these large scales of speed and mass, what happens to light? In his 1911-16 papers on the General Theory of Relativity, Einstein addressed the effect

of gravity on light. Gravity is described as distortions in the four dimensions of space and time (three dimensions for space and one for time), and such distortions define Newton's "force" of gravity–spacetime is actually curved. Because of this curvature, a beam of light passing near the sun would bend in the gravity of a massive object. Experimentally, it was found by Arthur Eddington during the 1919 eclipse that indeed light was bent as it passed by the sun, as predicted by the theory. In 1922, Einstein received the 1921 Nobel Prize, not for his theory of relativity but for the photoelectric effect, a contribution that elucidated one of the two characteristics (duality) of light–a bundle of particles of quantized energy.

Symmetry of Time

Even if we consider the "normal world" when velocities, masses, lengths, and time are with no corrections–Newtonian Limits–and spacetime with no curvature, we still have problems with time, its direction and uncertainty. First let us consider the symmetry of time. Can time go forward and backward, or does it have a direction, an arrow?

In Newton's world, the motion of objects, like you and me, should follow "symmetry of time," that is, the equations describing motion on say the human scale, or that of the Earth around the sun, are time symmetric. There is no difference in the way they work if we make the direction of time go "forward" or "backward." Newtonian mechanics are deterministic and time symmetric. Because the force is related to the mass and the acceleration ($F=ma=m(d^2x/dt^2)$), the equation works equally well for positive and negative time. So, calculating the future of a physical system from its present situation is the same as calculating its past physical situation from its present one–weird and contrary to our common sense. What about microscopic systems, for example the world invisible to the eye–the atom.

For quantum systems, the equation of motion also has invariance under time reversal insofar as the positions of microscopic particles are concerned. This is true despite the deceptive appearance of a first derivative in the Schrödinger wave equation that would imply time reversal. If you can magnify a box containing a gas and see the atoms hitting each other individually you will conclude that there is no arrow of time for every pair of collisions. So, in Newton's mechanics and quantum mechanics, time flows in both directions, making the apparent confusion for the meaning of past, present, and future! In our life, we feel the passage of time and we also know that matter is made of atoms, so we have a dilemma.

Arrow of Time

Phenomena in our life follow an arrow of time. A cup of hot water with a piece of ice displays melting of the ice–the ice does not spontaneously reform again; heat always flows from a hotter object to a cooler one, and not the reverse. An egg breaks when it hits the floor, but it cannot be reformed from the floor. These and similar phenomena are described by the most powerful law, or what Arthur Eddington called the "supreme law of Nature"–the second law of thermodynamics. In one way it describes the arrow of time. In another way, it tells us about the content of information–there is a natural tendency for systems in change to become less ordered or more disordered. A measure of this change is called entropy which is defined as a negative measure of information. Entropy always increases (or at best does not change), order decreases, information decreases, and complexity decreases.

But this loss of information and increase in entropy is for the so-called closed systems (the ice and hot water form a closed system). In some cases, order is created of disorder, and it appears at first that this is in violation of the law of entropy. The tree is a good example–light from the sun, soil and water, and by photosynthesis we have an ordered tree. The Earth is not a closed system and is a part of the solar system–the local decrease in entropy for the tree is compensated for by the way solar (and other) energy change its entropy, and for the solar system on a whole, entropy is increasing according to the second law.

If entropy is always increasing in our universe and the arrow of time is well defined from past to future, why do individual particles, constituents of matter, follow trajectories that are symmetric in time? Put another way, why for a collection of particles each obeying time-reversal symmetry the ensemble as a whole defines an arrow of time? Imagine a box divided into two halves with a partition, one half contains a gas and the other is empty. If we remove the partition the gas will move and fill the whole box. Entropy increased and it appears that we can never reverse the process–we cannot make the gas go into one half and then reinstall the partition to acquire the originally ordered state. In the gas box each particle has a trajectory that follows Newton's mechanics. With time being symmetric, why then does the collection of these particles make the time unsymmetrical? This is a debatable subject and there are different views, one I find particularly interesting.

Time scales and recurrences in time

In the nineteenth century, Henri Poincaré considered this problem of a gas in a box, with all possible arrangements of the particles. He concluded that the system, *if we wait long enough*, will return back to the initial state. The time for this Poincaré recurrence is vastly different depending on the system under consideration. For the gas in the box, the recurrence time for reordering all particles is longer than the age of the universe, but for the vibrational motions of atoms and molecules it could be a

millionth of a millionth of a second. This concept of time scale could explain the apparent behavior of systems, reversible or irreversible, depending on complexity and the number of possible arrangements or configurations.

This view is perhaps most clearly demonstrated on quantum systems with time scales short enough that we can experiment with them. If we take the same gas in the box and replace the hypothetical particles with shaped molecules we can perform an interesting experiment. To start with, we already know that there is no order in orientation of molecules and entropy is maximum. We now preferentially excite some of these molecules with their head and tails oriented roughly north and south of the box (we can do so in the laboratory with lasers). If the laser is ultrashort in duration (this too we can achieve in the laboratory) the induced ordered orientation of the molecules will ultimately be maximum at time zero and will decay with time. We call this process of degrading order dephasing, as the whole ensemble of millions of molecules prepared becomes out of step (phase) with each other. However, if we wait for some time, the molecules will acquire back the initial orientation giving rise to Poincaré's recurrences.

Such recurrences have been observed in our laboratory and on an ensemble of millions of molecules. Furthermore, these molecules are complex in their structure and internal motions and experts will tell you that these recurrences should not occur in such systems. But this is not true, as the energy levels are commensurate or nearly so even in complex systems. The recurrences are spaced long enough in time that depending on the time scale of observation the behavior of the system will appear differently. If the time scale of observation is too short, the system would appear irreversible in its decay behavior, but if we wait until recurrences occur we can then see the reversibility behavior.

Irreversibility becomes apparent if the system is not isolated. When the system interacts with a foreign perturber (such as collisions with other molecules–a heat bath) then such recurrences become weak and the system appears irreversibly disordered. Thus without designed methods for introducing order (coherence) to the system and/or without probes for observing its time evolution of disorder (dephasing) we may be misled about the nature of the dynamics. This is critical for defining the meaning and control of complexity and the time scale for reversible/irreversible behavior. We shall come back to this point when we consider measurement of time and matter's time scale.

The above consideration of microscopic/macroscopic behavior considers the origin of irreversible behavior in large ensembles as due to statistical "averaging." As such the law of entropy increase becomes a statistical law. To Ilya Prigogine, however, the second law of thermodynamics is a fundamental law describing irreversibility of nature–the gas in the box will never rearrange again and the ice in the hot cup will never reform, no matter how long we wait. We are now entering a risky area of interpretations and I prefer to stop here until we see further experimental proof! What about the behavior of individual atoms in molecules and their time scale? And, can we observe them moving with order in the ensemble?

At the Limit of Time–Democritus' Atom

The motion of atoms in molecules is fundamental to all dynamic changes of matter, whether the change is physical, chemical, or biological. But these atoms move with awesome rapidity and on ultrashort scales of time and length. On these scales, it is not clear that we can treat them as real, classical objects. Clearly, we must measure the passage of time for atoms on the time scale of the motion, and we must develop the concepts for understanding localization of atoms in space and time. Can this be achieved at the limit of time for quantum atomic motions? If we do, we will then observe Democritus' atom in motion and as a real object, making the transformation from the microscopic (wave function description) to the macroscopic (particle description) a reality in real time.

At Caltech, we have been interested in this endeavor of developing ultrafast laser light to freeze the motion of atoms, to make a motion-picture film of molecules with a frame resolution of a femtosecond. A femtosecond is a millionth of a billionth of a second. In one second, light travels 300,000 km (186,000 miles), almost the distance from the Earth to the Moon; in one femtosecond, light travels 300 nanometers, the dimension of a bacterium, or a small fraction of the thickness of a human hair. In principle, with femtosecond timing, the atom's motion becomes visible, but how can we advance stop-motion photography to reach the scale of the atom?

In the nineteenth century, the motion of animals was recorded for the first time using light shutters and flashes. In France, Étienne-Jules Marey, a professor at the Collège de France, was working (1894) on a solution to the problem of action photography using *chronophotography*, a regularly timed sequence of images. Marey's idea was to use a single camera and a rotating slotted-disk shutter, with exposures on a single film plate or strip that was similar to modern motion picture photography. Marey applied his chronophotographic apparatus in particular to humans and animals in motion, and to a subject that had puzzled people for many years: the righting of a cat as it falls so that it lands on its feet. How does the cat do it? Does its motion violate Newton's laws of mechanics? Does the cat have some special, magical physiology or a command of some weird new physics or what?

By "slicing time" and freezing the motion during the fall, in the transition state of the righting, Marey was able to answer the questions. First, the cat rotates the front of its body clockwise and the rear part counterclockwise, a motion that conserves energy and maintains the lack of spin, in accordance with Newton's laws. It then pulls in its legs, reverses the twist, and with a little extension of the legs, it is prepared for final landing. The cat instinctively knows how to move, and high divers, dancers, and some other athletes learn how to move in the absence of torque (the pushing force that gives you momentum in one direction or another). However, scientists needed photographic evidence of the individual stopped-action steps to understand the mystery. The answer to the puzzle was that the moving body was not rigid, and Newton's laws prevailed. At the time, these observations were thought-provoking

and renowed scientists discussed in public their meaning and significance. J. Willard Gibbs gave a talk on December 4, 1894 before the Mathetical Club at Yale with the title "On motions by which falling animals may be able to fall on their feet." Marey's work and that of Eadweard Muybridge on the horse have changed the way we think of the behavior of animals (and humans) in motion.

For the world of atoms in molecules, if the above ideas of stop-motion photography can be carried over in a straightforward manner, then the requirements can be identified for experiments in femtochemistry–the field of studying molecular motions on the femtosecond time scale. The contrast in *length* and *time* scales for the motion of the cat and the atom is awesome (Figure 2.2). For a definition of 1 cm, a cat speeding at 2 m/s requires a time resolution of 0.005 second. But for a molecular structure in which atomic motions of a few angstroms (an angstrom, Å, is 10^{-8} cm) typically characterize chemical change, a detailed mapping of the motion will require a spatial resolution of less than 1 Å (about 0.1 Å). Therefore, the shutter time, or time resolution, required to observe with high definition atoms in motion at a speed of one kilometer per second (1000 m/s) is 0.1 Å divided by 1000 m/s, which equals 10^{-14} second or 10 femtoseconds—a million million times shorter than what was needed for Marey's (or Muybridge's) stop-motion photography. Although this was a central idea in the development of femtochemistry, we had to overcome a major dogma regarding the uncertainty principle!

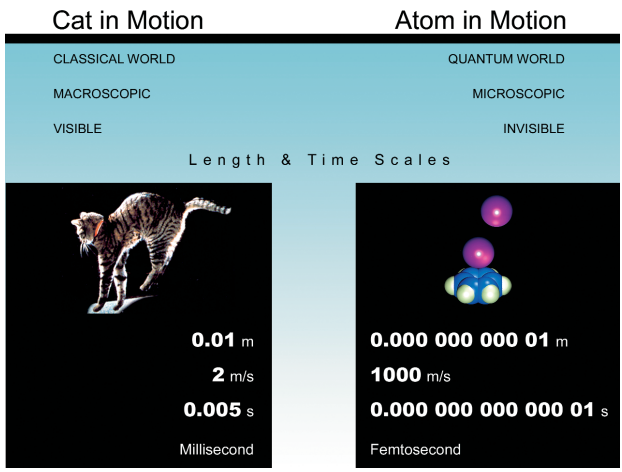


Figure 2.2. Length and time scales of atoms and cats.

Solving the Riddle of Uncertainty–Physics

For the atom such minute time and distance scales mean that molecular-scale phenomena should be governed by the principles, or language, of quantum mechanics, which are quite different from the familiar laws of Newton's mechanics that were used in the description of the motion of the cat and horse. Werner Heisenberg in the 1920s discovered that for quantum systems we are not allowed to make a precise measurement of both the position (x) and the momentum (p) of a particle at the same time. This tells us that we are losing knowledge – we do not know exactly where it is and where it is going (future), simultaneously, that is, the more accurately we determine one of these conjugates the more information we lose on the other. There is intrinsic uncertainty! Similarly, if we can measure the energy (E) of a system very precisely we cannot obtain the same precision for time (t) simultaneously. There is uncertainty in the measurement of time depending on how accurate the energy is, and the consequences are important for all sciences on the ultrashort time scale.

These considerations of uncertainties led initially to the belief that the femtosecond time resolution would not be useful. Moreover, predictions suggested that localization of atoms in space–wave packets–would not be possible to sustain for a long time, even on the femtosecond scale. Finally, there is a fundamental difference in the analogy between femtosecond stop-motion action of atoms and the millisecond photography of a cat or horse-in femtochemistry experiments one probes typically millions to trillions of molecules, and/or repeats the experiment many times to provide a signal strong enough for adequate images. Unlike experiments on one cat or one horse, the picture for an ensemble of molecules would be blurred.

We accommodate this by recognizing two of the most powerful and yet indigestible concepts: the uncertainty principle and the particle-wave duality of matter (de Broglie, 1924). The complementary aspect of these two descriptions is interwoven with the concept of coherence. Two or more waves can produce interference patterns when their amplitudes add up coherently. For matter, superpositions analogous to those of light waves can be formed from matter wavefunctions. The Schrödinger equation yields wavefunctions together with their probability distributions, which are diffuse over position space. But if these waves are added up coherently with well-defined phases, the probability distribution becomes localized in space. The resultant wave packet and its associated de Broglie wavelength has the essential character of a classical particle: a trajectory in space and time with a well-defined (group) velocity and position–a moving classical marble but at atomic scale.

To see motion in real systems, localized wave packets must form in every molecule, and there must also be a limited spread in position among the wave packets formed in the millions of molecules studied. This is achieved by the well-defined initial equilibrium configuration of the molecules before excitation and by the "instantaneous" femtosecond launching of the packet. The spatial confinement of the

initial ground state, typically 0.05 Å, ensures that all molecules, each with its own coherence, begin their motion in a bond-distance range much smaller than that of the actual motion, typically 5^{-10} Å. The femtosecond launching ensures that this narrow range of bond distance is maintained throughout preparation. With coherent and synchronous preparation, the motion of the ensemble becomes that of a single-molecule trajectory.

In 1987, we reached our goal of observing, for the first time, Democritus' atom—theorized by the Greek philosopher some 2500 years ago–in motion, and we could describe it on the femtosecond time scale as a classical object like the cat and horse (Figure 2.3). In reaching the femtosecond domain of the atom, with a scale of a millionth of a billionth of a second, the time resolution of today compared to that of a century ago, with a scale of a thousandth of a second, is like one day compared to the age of the universe.

Eugene Wigner and Edward Teller debated the uncertainty paradox for picosecond time-resolution in a lively exchange at the Welch Conference in 1972. But, because of coherence, the uncertainty paradox is not a paradox even for femtoscience, and certainly not for the dynamics of physical, chemical, and biological changes. Charles Townes encountered objections in the realization of the maser because of concern about the uncertainty principle, but coherence was again the key to success. As we cross the femtosecond barrier into the attosecond regime for studies of electron dynamics, we must recall this vital role of coherence. Otherwise the spectre of quantum uncertainty might veil the path to new discoveries.

In retrospect, this vital role of coherence in the uncertainty paradox and the fog that surrounded its utility should have been clear (Figure 2.3 and bibliography). We and others have considered in detail the theoretical quantum calculations of molecular systems and indeed confirmed the localized motions of atoms. But, the physical origin of the behavior is simple to understand. Considering the uncertainty in the position to be Δx, and similarly for the other variables, the two uncertainty relations,

$$\Delta x \, \Delta p \geq \hbar /2$$
$$\Delta t \, \Delta E \geq \hbar /2$$

show that the only way to localize atoms (small Δx) is by shortening time (Δt). Moreover, when Δt is on the femtosecond time scale, even a discrete quantum system, if excited coherently, becomes effectively a continuum or quasi-continuum of energy states, which represents a transition to the classical world.

Given that we can localize a system to an initial distance of Δx_o at time zero, why does the system remain coherent and behave as a classical object? And, does the time for the loss of coherence depend on the size of the object? Because the value of $\hbar$ is very small, this time depends crucially on the size. To see this clearly, we must recall that the uncertainty relation relates the uncertainty in position (Δx) to the uncertainty in momentum (Δp); but it is the velocity, and not momentum per se, which tells us the future position. Since $\Delta p = m \, \Delta v$, it follows, from the uncertainty relation, that $\Delta v = \hbar /(2m \, \Delta x_o)$–the larger the size (the larger the mass m and also the

larger the scale of precision in position Δx_o) the smaller the uncertainty in velocity (Δv) and the better we are in predicting the future. Now it is straightforward to calculate the "time of uncertainty" which tells us how long it will be before the uncertainty in velocity will contribute as much to our lack of knowledge of where the object is as that which came from the original position uncertainty (Δx_o):

$$t \text{ (uncertainty)} = \Delta x_o / \Delta v = 2m \, \Delta x_o^2 / \hbar$$

Beyond this time scale, the uncertainty, due to our lack of knowledge of velocity, makes us less certain of the future and the description of the object becomes quantum, not a classical one. This simplified equation can be obtained from a more rigorous treatment of wave packet motion, and elsewhere we did so.

The size of $\hbar$, 1 x 10^{-27} erg-sec, means that the fuzziness required by the uncertainty principle is imperceptible on the normal scales of size and momentum, but becomes important at atomic scales. For example, if the position of a stationary 200-g apple is initially determined to a small fraction of a wavelength of light, say Δx_o = 10 nm, the apple's position uncertainty will spread by about 40% only after 4 x 10^{17} s, or 12 billion years, that is, the age of the universe! On the other hand, an electron with a mass 29 orders of magnitude smaller would spread by 40% from an initial 1-Å localization after only 0.2 femtosecond.

From atom to man, the time and length of uncertainty determine the classical-quantum description of motion (Figure 2.4). The time scale for future uncertainty runs from femtoseconds for the hydrogen atom, to 300 years for biological cells, and to more than the age of the universe for humans–we have 300 years (or more) to behave in a deterministic classical world, so biotechnologists can be sure to improve the human life expectancy by at least three times from the current one without the need of new mechanics!

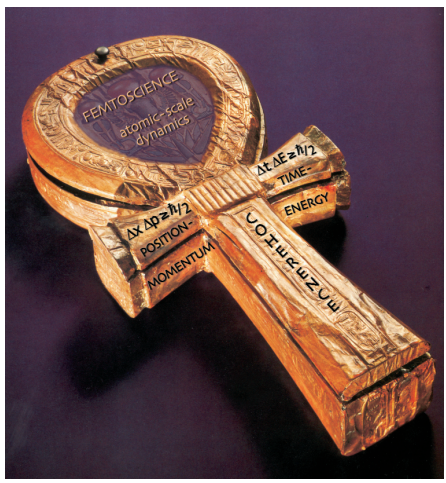


Figure 2.3. Uncertainties and unification through coherence.

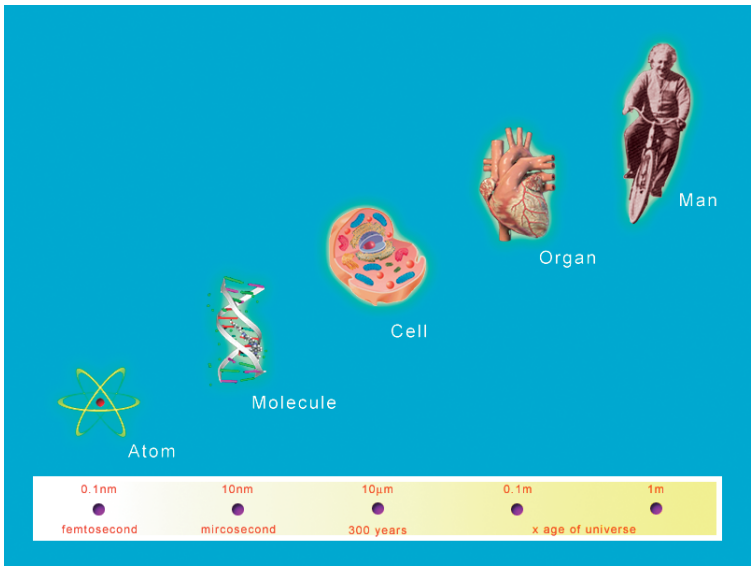


Figure 2.4. From Atom to Man- length scale and time of uncertainty.

The Molecular World–Chemistry

Conceptually, our work in the late 1970s on coherence phenomena and in the mid 1980s closing in to resolve reaction dynamics in real time provided the foundation for thinking about the issues raised above. It became clear that molecules can be made to vibrate coherently and ensembles of molecules can be made to behave in unison. Experimentally, we needed a whole new apparatus, a whole new "camera" with unprecedented time resolution. We needed to interface femtosecond lasers and molecular-beam technology, which required not only a new initiative but also a major effort at Caltech. In a relatively short time, femtochemistry research became active in many laboratories around the world.

The breadth of applications emerging spans the very small to very complex molecular assemblies, and all phases of matter. An example that demonstrates the unity of concepts from small to large molecular systems came from a paradigmatic study made at Caltech on a sibling of table salt (two atoms) and another at Berkeley on the protein molecule of vision (hundreds of atoms). In both, the primary step involves femtosecond motion of the atoms, and we now understand better the remarkably coherent and highly efficient first step of vision at the atomic level.

Complexity–Biology

An especially exciting frontier for femtoscience is in biology. At Caltech we now have the National Science Foundation's Laboratory for Molecular Sciences (LMS) for interdisciplinary research on very complex systems. Among the recent new studies published in femtobiology are those concerned with the conduction of electrons in the genetic material, the binding of oxygen to hemoglobin (myglobin) and its mimics, molecular recognition of protein by drugs, and the molecular basis for the cytotoxicity of anticancer drugs, and of digestion.

A current major problem of interest is the role of water in biological systems–biological water. The pertinent question is: How does the interaction of water molecules with proteins and DNA influence the biological function? In a series of papers we have reported our studies of interfacial water dynamics and the unique role the dynamics play in the function. We are also developing new techniques to observe the behavior and architecture of these complex molecules–in space and time–using diffraction images, which give the 3-D location of all the atoms, all at once. But now a fourth dimension–time–is introduced to see how complex systems behave during the function. The new methodology, which we termed ultrafast electron crystallography (and microscopy), is now established with many applications (see bibliography). The impact on biology and medicine is clear.

Life is a manifestation of complexity in which atoms of the microscopic world combine in different ways to form functional systems with enormous diversity and unique information. And that is what makes the human "intermediate scale" (Figure 2.1) special–on one hand simple in function and on the other hand rich in complexity. Deciphering this complexity and reducing its meaning to the atomic motions involved is one of the most fundamental problems of this century.

Technology of Femtoscience

As for technology developments–femtotechnology–there are exciting new developments in microelectronics (femtomachining), femtodentistry, and femtoimaging (microscopy) of cells and tumors, not to mention possible new developments with intensities reaching that of the sun (in femtoseconds!) and duration going beyond the femtosecond (attosecond), and the interface with nanoscience and technology–marrying scales of time and length. The ability to count optical oscillations of more than 10^{15} cycles per second will lead to the construction of all-optical atomic clocks, which are expected to outperform today's state-of-the-art cesium clocks, with a new precision limit in metrology. There is also the potential for using powers reaching 10^{20} watts/cm^2 to induce nuclear fusion in clusters of atoms through Coulomb explosion. There is also the possibility for controlling matter on the femtosecond time scale–one day we may direct chemical reactions into specific or new products.

Epilogue

I wish to conclude by conjecturing on some future mysteries and miracles of time. In the physical sciences, one advance that surely will allow us to reach the electron domain involves measurements on the sub-femtosecond time scale. Now the average energy is nearing the x-ray region, much above chemical and biological energies, and the pulse width is larger than chemical binding energies. Nonetheless, such advances will make it possible to study electron dynamics in many domains of physics and related areas.

In the life sciences, the advent of diffraction and microscopy techniques with atomic-scale spatial and temporal resolution will undoubtedly lead to a revolution in structural dynamics of biomolecules, building real bridges between structures, dynamics and functions (see bibliography).

In cosmology, Planck's scale of time, the nature of spacetime, and the arrow of time are subjects that will remain in need of further discovery and search for meaning.

From the very small (atom), to the very complex (life), to the very big (universe), despite some mysteries, new frontiers will be reached with time defining a fundamental dimension. Perhaps the biggest of all challenges is reversal of time. Ever since H. G. Well's novel "The Time Machine," the human imagination has considered the possibility of reversing the arrow of time, going back in time. In theory we could, but the paradoxes are many. A time traveler may go back in time and alter circumstances leading to his own existence or lack thereof. Two-way time travel is indeed weird, and may force an entry to the world of weird physics! So despite its miracles and the impact on our life, we still struggle with the meaning of time.

Bibliography

Albert, David. 2000. Time and Chance. Harvard University Press, Cambridge.

Barrow, John D. 2002. The Constants of Nature. Pantheon Books, New York.

Gribbin, John. 1998. In Search of the Big Bang (new edition), Penguin Books, New York.

Hall, Nina. 2002. Chemistry and Biology in the New Age. Chem. Commun. (Feature Article, Ahmed Zewail), October 7 issue, 2185.

Hazen, Robert M., and James Trefil. 1996. The Physical Sciences. John Wiley & Sons, New York.

Ihee, H., V. Lobastov, U. Gomez, B. Goodson, R. Srinivasan, C.Y. Ruan, and A.H. Zewail. 2001. Direct Imaging of Transient Molecular Structures with Ultrafast Diffraction. Science, 291, 385.

March, Robert. 1978. Physics for Poets, Contemporary Books, Chicago.

Ruan, C.Y., V. Lobastov, F. Vigliotti, S. Chen, and A.H. Zewail. 2004. Ultrafast Electron Crystallography of Interfacial Water. Science, 304, 80.

Zewail, A.H. 2004. Femtochemistry–Atomic-Scale Dynamics of the Chemical Bond Using Ultrafast Lasers. Les Prix Nobel, The Nobel Prizes, Almquist & Wiksell International, Stockholm.

Zewail, A.H. 2001. The Uncertainty Paradox–The fog that was not. Nature, London, 412, 279.

Zewail, A.H. 2002. Voyage Through Time–Walks of Life to the Nobel Prize. American University Press, Cairo (also in 12 editions and languages).

Zewail, A.H. 2005. Diffraction, Crystallography, and Microscopy Beyond 3D–Structural Dynamics in Space and Time. Philosophical Transactions, Royal Society, 364, 315.

Chapter 3

Science and Society: Some Reflections

Jean-Marie Lehn

Introduction

BioVision Alexandria 2004 provided a unique occasion to revive the tradition of the Museion and of its great thinkers including Euclid, Erastosthenes, Archimedes, Hipparchos, Herophilus (already a life scientist), and many other founders of science, who developed the rational approach to the universe and its contents, including humans.

Hypatia, the last recorded scholar in Alexandria, the first woman in mathematics and astronomy, a neo-Platonist philosopher, was murdered in 415 AD. In her image, we as present-day scientists have the mission to further science and knowledge, to spread rationality, tolerance, and understanding, to make the world a better place to live for all human beings.

Bibliotheca Alexandrina is dedicated to the celebration of human knowledge. BioVision Alexandria 2004 paid special attention to developing regions of the world, and to North-South and South-South issues. We gathered for Life Sciences, but we addressed Living Science.

Science offers most exciting perspectives for the future generations. It promises a more complete understanding of the universe, an always greater creative power over the structure and transformations of the inanimate as well as of the living world. It also promises an increasing ability to take control over disease, ageing and even over the evolution of the human species, including a deeper penetration into the working of the brain, the nature of consciousness, and the origin of thought.

Among all the areas of knowledge that constitute science, biological sciences and technologies are providing entirely new perspectives to our understanding and action of the living world, for health care, food production, and environmental control. They will have strong impact on social and personal relationships, family structure, law, and ethical values.

The technologies of life, resulting from the extraordinary progress made in understanding life processes and the ability to act upon them, appear to tamper with a basic mystery and to lift and interdict with the risk of unleashing uncontrollable forces. The potential of genetic engineering has aroused many reservations, in some

countries more than in others. But the benefits that it can bring are countless, in agriculture and food production for instance, but above all to human health. Substances extracted from natural sources may be contaminated by compounds that present risks to health. Biotechnologies may permit us to circumvent the problem. Thus, synthetic vaccines may be safer than natural ones. The production of human growth hormone by genetic engineering gives a product devoid of the prion that infects the same substance of natural origin and causes the Creutzfeld-Jakob disease. Numerous other such cases can be found, one being the production of factor VIII for blood transfusion without risk of infection by HIV. Other examples would be the engineering of bananas containing vaccines or of vegetables producing contraceptives that would allow women in developing countries to control their fertility. Stem cell research also opens fantastic perspectives to biology and biotechnology.

Zero risk does not exist. Risk appears with life. Zero risk is a dead world. The desire to systematically eliminate all risk also destroys opportunities and may as well become a threat to freedom and democracy.

Our duty is to optimize the chances and minimize the risks.

Our descendants will continue to evolve intellectually, culturally, and materially. They may, with hindsight, adopt points of view quite different from ours. To stop this would deprive them of the possibility of further development and would prevent them from succeeding where we failed. We must offer them all the chances and transfer to them all the powers. This is our responsibility, and we have no right to hand down judgments in their place. They may be wiser than we are.

Molecular Chemistry

Molecular chemistry has developed a wide range of powerful procedures for building ever more complicated molecules from atoms linked by covalent bonds. Beyond molecular chemistry lies supramolecular chemistry that aims at constructing highly complex chemical systems from components held together by intermolecular forces.

Numerous receptors capable of selectively binding specific substrates have been developed. They perform molecular recognition that rests on the molecular information stored in the interacting species. Suitably functionalized receptors may perform supramolecular catalysis and selective transport processes. In combination with polymolecular organization, recognition opens ways to design molecular and supramolecular devices based on functional (photoactive, electroactive, ionoactive) components.

Supramolecular chemistry has relied on more or less preorganized molecular receptors for effecting such molecular recognition, catalysis, and transport processes. A step beyond consists in the design of systems undergoing self organization, that is systems capable of spontaneously generating well-defined supramolecular architectures by self assembly from their components. Self organization processes

may be directed via the molecular information stored in the covalent framework of the components, and read out at the supramolecular level through specific interactions. They thus represent the operation of programmed chemical systems.

A number of investigations have been performed at the interface between supramolecular chemistry and biology. They concern developments in areas such as: optical sensing of biomolecular recognition, medical diagnostics based on photonic molecular devices, modified liposomes bearing recognition groups (recosomes), dynamic combinatorial chemistry for drug research, gene transfer methodology, and self assembly processes.

Benefits to Developing Countries

A crucial question concerns the developing countries. Will the gap that separates them from industrial countries get wider and wider? A continuing and aggravating problem into the century is the unacceptable North/South imbalance and the resulting strains. It is the responsibility of the industrial countries to offer solutions and strive for "sustainable development" for everybody on earth.

One may hope that the accumulated knowledge and the very efficient advanced technologies resulting from research in the industrial countries might provide means for the less advanced ones to enter directly into a "high tech" era. This would be based on highly advanced technologies that are more economical and much less demanding in raw materials, resources, and energy.

For instance, a country that has an unsatisfactory telephone system will not have to lay more wires but can directly go to cellular phones, and may thus even be at an advantage over countries having a developed classical phone network. Telemedicine, telesurgery are other examples; a physician in a remote area of the world will have the possibility to obtain guidance and advice from specialists in industrial countries.

Promoting Science

Science education in our schools, colleges, and universities as well as for the general public must be a major priority, to train the researchers and discoverers of tomorrow. This would remove irrational fears and rejections, and develop the scientific spirit, the scientific attitude, to fight the obscure, the deceitful, and the irrational.

Beyond the general progress of knowledge and the technological development, the most important impact science can and must have on society is the spirit that it implies, the scientific, rational approaches toward the world, life, and society. This is an area in which the Bibliotheca Alexandrina can play a major role, in particular for developing countries.

Education, science and technology may collide with tradition and hurt beliefs or social structure. We must be prepared for that and take it into account so as to

overcome it. The installation of a solar-powered water pump accessible to everybody in a village of a developing country may destroy a traditional structure where power was in the hands of those who controlled the water supply. Thus, science brings new freedoms but mankind has to learn to live with them.

Bioethics

An important issue for scientists is ethics, and more specifically bioethics. The scientist has a general responsibility to the truth, and only then is there responsibility to the society and the world. Ethics is a function of time, location, and knowledge. Pursuit of knowledge and truth supersedes present considerations on what nature, life or the world are or should be, for our own vision can only be a narrow one. Ethical evaluation and rules of justice have changed and will change over time.

With all the caution that must be exercised, and despite the risks that will be encountered, carefully pondering each step mankind must and will continue along a path, for we have no right to switch off the lights of the future.

These perspectives for the future of science, for our future, have already been expressed in most fitting terms by the artist-scientist Leonardo da Vinci when he wrote: “Where nature finished to produce its own species, man begins, using natural things, with the help of this nature, to create an infinity of species.”

Prometheus conquered fire and we cannot give it back. We have to continue from the tree of knowledge to the control of destiny.

General References

Lehn, J.-M. 1995. Supramolecular Chemistry: Concepts and Perspectives. VCH Weinheim.

Lehn, J.-M. 1996. Science and Society. The natural-unnatural dualism. Interdisciplinary Science Reviews, 21: 103.

Lehn, J.-M. 2002. “Toward complex matter: Supramolecular chemistry and self-organization.” Proc. Natl. Acad. Sci. USA, 99, 4763.

Lehn, J.-M. 2002. “Toward self-organization and complex matter.” Science, 295, 2400.

Chapter 4

Asymmetric Catalysis: Roles In Biomedical Science and Technology

Ryoji Noyori

Introduction

In concert with the recent mapping of the human genome sequences, scientists started to intensively investigate the structures and functions of the corresponding proteins. One of our major goals is to develop effective pharmaceutical drugs that prevent or cure painful diseases. Pharmaceutical drugs are precisely structured organic compounds that are compatible with proteins or other large biomolecules in human bodies. They mostly have a low molecular weight, <500, and are largely synthetic rather than natural. The world pharmaceutical market has been growing steadily, and some important drugs have achieved huge worldwide sales. For example, Simvastatin, $C_{25}H_{37}O_5$, manufactured by Merck Company, is an excellent drug for hypercholesterolemia. Annual sales exceed US$5 billion.

Role of Chemistry

Our concern is: how do we efficiently discover and economically synthesize such important compounds? The biochemical information of protein structures obviously helps the development of potent pharmaceutical drugs. I emphasize that chemistry plays a crucial role in the discovery, research, and production of such significant compounds. Without chemical synthesis, the pharmaceutical industry would not exist.

The major concern of chemists is molecules and molecular assemblies. Any molecule, by definition, has a fixed elemental composition, a definite atom connectivity, a single configuration, and some conformations. On the basis of such structural characteristics, interesting and significant molecular functions emerge. Most importantly, in principle, any molecule can be designed and synthesized as desired. Thus, a diverse array of properties and functions can be generated by utilizing accumulated chemical knowledge. Chemistry is a science not only

concerned with the observation and understanding of nature but is characterized by the capability of producing highly valuable compounds from almost nothing.

I have been interested in the molecular chirality of organic compounds (Noyori, 2002). Molecular chirality normally emerges when a carbon atom possesses four different atoms or groups, resulting in two stereoisomers, called enantiomers (R and S), that are mirror images of one another and have identical free energy. The differences between enantiomers are slight, but become important when they are involved in biological or physiological phenomena. Enantiomers often taste and smell different. For example, (S)-glutamic acid monosodium salt is tasty, while the R form is bitter. (R)-Limonene has the fragrance of orange, while its S isomer has that of lemon. (S)-Carvone has a fragrance of caraway seeds, while its R isomer has a component of spearmint and smells completely different. These phenomena are based on precise molecular interactions between such small chiral molecules and large protein receptors in our bodies, where the molecular chirality plays a key role.

The structural differences between them may have deleterious effects in the case of synthetic drugs. An example of the incompatible relationship between molecular chirality and pharmacological activity was provided by the tragic administration of thalidomide to pregnant women in the 1960s. The commercial thalidomide is a 50:50 (racemic) mixture of right- and left-handed enantiomers. (R)-Thalidomide has desirable analgesic properties, while its S enantiomer is a teratogenic and induces fetal malformations. Although there still exists a controversy in this interpretation, such problems arising from inappropriate molecular recognition in the human body must be avoided at all costs. Thus, the selective chemical synthesis of enantiomers, called asymmetric synthesis, is crucial in the pharmaceutical industry. However, until recently this remained extremely difficult. In 1990, approximately 1800 pharmaceutical drugs were on the market. They come from various sources and have different chiralities. It should be noted that 88% of the synthetic chiral drugs were sold still in the racemic form, despite the thalidomide tragedy. Then, in 1992, Federal Drug Administration of the USA introduced guidelines on “racemic switch,” encouraging the commercialization of enantiomerically pure drugs produced by practical asymmetric synthesis. As a consequence, the proportion of enantiomerically pure drugs increased up to 40%, thanks largely to the efforts of synthetic organic chemists.

Asymmetric Catalysis

To achieve this we require some general principles. Our method is to use a chiral molecular catalyst that consists of a metallic element and an attached chiral ligand, as schematically illustrated in Noyori (1994). The active metal center generates catalytic reactivity, accelerating a reaction repeatedly, while the attached chiral ligand controls stereoselectivity in the absolute sense. Our concerns are twofold. First, we must address the productivity and rate of a reaction; how many times does

the catalyst turn over and how fast is the reaction? Second, we are concerned about the extent of enantioselectivity, which ranges from 50:50 (nonselective) to 100:0 (perfectly selective). Asymmetric catalysis is four-dimensional chemistry (Noyori, 1994). Thus a high efficiency can be achieved using a combination of both an ideal three-dimensional structure (x, y, z) and suitable kinetics (t) (Noyori *et al.,* 2004). This is a general principle of asymmetric catalysis that is widely practiced in organic synthesis. Indeed, we were the first to discover this principle in 1966 (Nozaki *et al.,* 1966).

In 1980 after six years of effort, we reported for the first time the synthesis of the BINAP/Rh complex (Miyashita *et al.,* 1980). This beautifully shaped chiral molecular catalyst became famous when we applied it to the industrial synthesis of menthol, a popular fragrance. Thus, when geranyldiethylamine is exposed to a small amount of the (S)-BINAP/Rh complex, (R)-cintonellal diethylenamine is obtainable in >98% ee (ee = enantiomeric excess, (R - S)/(R + S)) (Tani *et al.,* 1982). This reaction is highly productive and applicable to a 9-metric-ton scale. This is the result of a fruitful academic/industrial collaboration between the universities of Shizuoka, Osaka, and Nagoya, the Okazaki Institute for Molecular Science, and Takasago International Corporation. Takasago produces various optically active terpenes, including 1000 tonnes of (-) -menthol per year, corresponding to one-third of the world's demand (Akutagawa, 1992).

Assymmetric Hydrogenation

This asymmetric allylamine-enamine double bond-shift reaction is a very important process but is rather unconventional. Then we decided to pursue a more common asymmetric catalysis, namely, asymmetric hydrogenation. H_2 is the simplest molecule and a clean and abundant resource. H_2 has unlimited applicability to basic and applied science, technology, and even industry. Although the hydrogenation of unsaturated compounds is the most fundamental chemical reaction, efficient methods remain limited. For more than two decades since 1980, we have developed a series of chiral BINAP/transition metal complex catalysts for asymmetric hydrogenation (Noyori, 1989, 1990, 1992, 1994, 1996, 2002; Noyori and Ohkuma, 2001; Noyori and Takaya, 1990). A major breakthrough occurred in 1986 when we developed the BINAP/Ru dicarboxylate complexes (Noyori *et al.,* 1986). Ru behaves differently from conventional Rh, allowing the selective synthesis of many enantiomeric compounds. The enantioselection is very distinct, often >99:1 and even 100:0.

The utility of the Ru complexes is extensive. Previously we noted that the BINAP/Rh complex catalyzes the asymmetric hydrogenation of a dehydro amino acid derivative to yield the phenylalanine derivative in nearly 100% ee (Miyashita *et al.,* 1980). However, the reaction was slow, and the scope of the olefinic substrates was narrow. Fortunately when Rh was replaced by Ru, the scope could be extended

significantly, allowing the asymmetric hydrogenation of many types of olefinic substrate. For example, reaction with N-acylated benzylidene-tetrahydroisoquinolines yielded the benzyl-tetrahydroisoquinolines in near 100% ee, providing a general method of the asymmetric synthesis of isoquinoline alkaloids (Kitamura *et al.*, 1994). Hydrogenation of the acrylic acid with an aromatic ring gave the anti-inflammatory (S)-naproxen in 97% ee (Ohta *et al.*, 1987). When geraniol was used as a substrate, hydrogenation occurred only at the allylic alcohol part, giving citronellol in more than 95% ee (Takaya *et al.*, 1987). It is now possible to hydrogenate many other olefinic substrates using the new BINAP/Ru complexes. Most importantly, the list of potential substrates can even be extended to include various ketones (Kitamura *et al.*, 1988). The catalyst is BINAP/Ru dichloride or dibromide, and the presence of halogen atoms is also crucial for the catalytic activity. β-Keto esters are the best substrates for the BINAP/Ru-catalyzed asymmetric hydrogenation (Noyori *et al.*, 1987). This method is superior to any other chemical or biological synthetic procedures, and it allows the synthesis of various chiral β-hydroxy esters. This process can be performed at a very large scale (Noyori, 1992). For example, carbapenem antibiotics are now best synthesized by this asymmetric hydrogenation. In the presence of the (R)-BINAP/Ru complex, racemic methyl α-(benzamidomethyl)acetoacetate (a chiral β-keto ester) is hydrogenated to give the R,S-configured β-hydroxy ester under dynamic kinetic resolution (Noyori *et al.*, 1989, 1995). The erythro:threo diastereoselectivity is 94:6 and the 2S,3R:2R:3S enantioselectivity is 99.5:0.5 (99% ee). This compound is now produced in large quantities at Takasago International Corporation. In addition, the simple asymmetric hydrogenation of acetol to (R)-propanediol is employed for the synthesis of levofloxacin, a very important antibacterial agent developed at Daiichi Pharmaceutical Company in Japan.

Hydrogenation of Simple Ketones

Furthermore, we recently devised new catalysts that allow rapid, productive and selective hydrogenation of simple ketones, which is otherwise difficult to achieve (Noyori and Ohkuma, 2001). For example, 600 g of acetophenone can be hydrogenated with only 2 mg of the well-designed chiral BINAP/1,2-diphenylethylenediamine Ru catalyst (Doucet *et al.*, 1998). A single molecular catalyst has an overall turnover number of more than two million times and a turnover frequency of 60 times per second. The high efficiency is due to the operation of a nonclassical metal-ligand bifunctional mechanism. Molecular hydrogen is symmetrical. However, upon interaction with our Ru catalyst, the H-H bond is cleaved and asymmetrically activated, and the resulting species reduces ketones with high enantioface distinction. This process is repeated more than two million times.

Our method is already at a very advanced technical level and some compounds are now produced in industries. This asymmetric hydrogenation provides a powerful tool for producing important chiral compounds.

How do we discover such important compounds? As mentioned above, pharmaceutical drugs are relatively small, precisely structured artificial organic compounds. The discovery of effective drugs requires a global approach involving the fields of chemistry, biochemistry, pharmacology, clinical medicine, and computer science, and the use of various efficient analytical and diagnostic instruments. The development of drugs often requires a ten-year research period, up to 400 researchers in various fields, and an enormous cost as high as US$0.5-1 billion per drug. In addition, a range of the latest scientific information and the most advanced technologies are necessary.

The current most serious problem is the high cost of pharmaceutical drugs. This is a problem in many countries. The market of pharmaceutical drugs in Japan is currently about US$60 billion, which contributes considerably to the total expenses for the national medical care system of up to US$300 billion. Therefore, a significant issue is how do we decrease the high costs of developing new pharmaceutical drugs. Without a significant decrease, modern pharmaceutical drugs can be used only in rich, advanced countries but, unfortunately, not in developing countries. One of the major reasons for the high cost is that currently about 90% of candidate drugs are excluded during the clinical trials, due to their toxicity and/or unfavorable pharmacokinetics. Although various efforts should be made to decrease such a serious financial risk, we propose a possible scientific/technical way to achieve this goal.

We became interested in applying our asymmetric prostaglandin synthesis (Noyori and Suzuki, 1984, 1990) to the science of the human brain. In this context, we have established a fruitful interdisciplinary and international collaboration with Professor Suzuki, a long-term collaborator now at Gifu University, Professor Watanabe, a biomedical researcher at Osaka City University, and Professor Långström at Uppsala University (Takechi *et al.*, 1996; Suzuki *et al.*, 2000b). We found that the prostacyclin-type carboxylic acid (R = H), called (15R)-TIC, shows a strong, selective binding to certain receptors in the central nervous system. The unnatural R configuration is important and accessible using our asymmetric chemical method. This was discovered during an *in vitro* study using tritium-labeled (15R)-TIC and frozen sections of a rat brain. However, this compound is not appropriate for investigations in the human brain, since β^--particles from tritium cannot penetrate human tissues. For this reason, we wanted to incorporate 11C into the aromatic group allowing noninvasive PET studies. The very short half-life of ^{11}C, 20 minutes, is beneficial but leads to a new chemical problem. Thus, although the $^{11}CH_3$ group must be incorporated in the final step of the synthesis of (15R)-TIC methyl ester, the total time for the synthesis, workup, purification, and sterilization should be less than 40 minutes.

One of my students made a tremendous effort to solve this problem and found a method of incorporating a methyl group in the aromatic ring within 5 minutes (Suzuki *et al.*, 1997, 2000a). This technology was then transferred to the PET center at Uppsala University, where Professor Suzuki volunteered as a subject for testing this new compound. The ^{11}C-labeled (15R)-TIC methyl ester, which was intravenously administered to his right arm, was carried by the bloodstream, passed through the blood-brain barrier, reached his brain, and was hydrolyzed to the free carboxylic acid, which was finally bound to IP_2 receptors in his central nervous system. The clinical significance of this behavior is not yet clarified. However, an *in vitro* study indicated that this compound suppresses the death of neurons under a high oxygen concentration.

The principle of PET is simple. A ^{11}C nucleus undergoes β^+ decay forming ^{11}B and a positron with a half-life of 20 minutes. The positrons collide with neighboring electrons and disappear, resulting in the emission of intense gamma rays of 511 keV. The measurement and computer analysis of these gamma rays result in a molecular imaging of the drug in the human body. Notably, ^{11}C has a very high specific radioactivity and a very short half-life of approximately 20 minutes. Most importantly, this method is noninvasive and negligibly harmful. This analysis is performed by microdosing of a drug and also outside the living human body. The extensive use of PET for research must be beneficial for developing new pharmaceutical drugs. In Japan, the PET technology is extensively used for diagnosis but, unfortunately, not at all in research for drug discovery. This noninvasive approach is crucial for developing evidence-based medicines. In addition, I am certain that the application of this method at an early stage of a clinical trial contributes to a decrease in the total cost of drug development.

Conclusion

The roles of asymmetric catalysis in biomedical science and technology are significant (Noyori, 2002). Well-designed chiral molecular catalysts permit the chemical synthesis of various bioactive compounds and functional materials. Asymmetric syntheses can be performed on a very large scale, as in the case of menthol synthesis, whereas brain research can be carried out on a very small, subfemtomole scale. In all cases, further studies of molecular chirality promise to yield great clinical and scientific benefits in the years to come.

References

Akutagawa, S. 1992. Practical Asymmetric Syntheses of (-)-Menthol and Related Terpenoids. Organic Synthesis in Japan. Past, Present, and Future. Noyori, R. (Editor-in-chief), Tokyo Kagaku Dozin, Tokyo, p. 77.

Doucet, H., T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A.F. England, T. Ikariya, and R. Noyori. 1998. trans-[RuCl2(phosphane)2(1,2-diamine)] and Chiral trans-[RuCl2(diphosphane)(1,2-diamine): Shelf-Stable Precatalysts for the Rapid, Productive, and Stereoselective Hydrogenation of Ketones. Angew. Chem., Int. Ed. Engl., 37, 1703.

Kitamura, M., Yi. Hsiao, M. Ohta, M. Tsukamoto, T. Ohta, H. Takaya, and R. Noyori. 1994. General Asymmetric Synthesis of Isoquinoline Alkaloids. Enantioselective Hydrogenation of Enamides Catalyzed by BINAP–Ruthenium (II) Complexes. J. Org. Chem., 59, 297.

Kitamura, M., T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, and R. Noyori. 1988. Homogeneous Asymmetric Hydrogenation of Functionalized Ketones. J. Am. Chem. Soc., 110, 629.

Miyashita, A., A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, and R. Noyori. 1980. Synthesis of 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), an Atropisomeric Chiral Bis(triaryl)phosphine, and Its Use in the Rhodium(I)-Catalyzed Asymmetric Hydrogenation of a-(Acylamino)acrylic Acids. J. Am. Chem. Soc., 102, 7932.

Noyori, R. 1989. Chemical Multiplication of Chirality: Science and Applications. Chem. Soc. Rev., 18, 187.

Noyori, R. 1990. Chiral Metal Complexes as Discriminating Molecular Catalysts. Science, 248, 1194.

Noyori, R. 1992. Asymmetric Catalysis by Chiral Metal Complexes. Chemtech, 22, 360.

Noyori, R. 1994. Asymmetric Catalysis in Organic Synthesis, John Wiley & Sons, New York.

Noyori, R. 1996. Asymmetric Hydrogenation. Acta Chem. Scand., 50, 380.

Noyori, R. 2002. Asymmetric Catalysis: Science and Opportunities (Nobel Lecture). Angew. Chem., Int. Ed., 41, 2008.

Noyori, R., T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, S. Saito, T. Taketomi, and H. Kumobayashi. 1989. Stereoselective Hydrogenation via Dynamic Kinetic Resolution. J. Am. Chem. Soc., 111, 9134.

Noyori, R., M. Kitamura, and T. Ohkuma. 2004. Toward Efficient Asymmetric Hydrogenation: Architectural and Functional Engineering of Chiral Molecular Catalysts. Proc. Nat. Acad. Sci., 101, 5356.

Noyori, R. and T. Ohkuma. 2001. Asymmetric Catalysis by Architectural and Functional Molecular Engineering: Practical Chemo- and Stereoselective Hydrogenation of Ketones. Angew. Chem., Int. Ed., 40, 40.

Noyori, R., T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, and S. Akutagawa. 1987. Asymmetric Hydrogenation of b-Keto Carboxylic Esters. A Practical, Purely Chemical Access to b-Hydroxy Esters in High Enantiomeric Purity. J. Am. Chem. Soc., 109, 5856.

Noyori, R. and M. Suzuki. 1984. Prostaglandin Syntheses by Three-Component Coupling. Angew. Chem., Int. Ed. Engl., 23, 847.

Noyori, R., M. Ohta, Yi. Hsiao, M. Kitamura, T. Ohta, and H. Takaya. 1986. Asymmetric Synthesis of Isoquinoline Alkaloids by Homogeneous Catalysis. J. Am. Chem. Soc., 108, 7117.

Noyori, R. and M. Suzuki. 1990. An Organometallic Way to Prostaglandins: The Three-Component Coupling Synthesis. Chemtracts–Org. Chem., 3, 173 .

Noyori, R. and H. Takaya. 1990. BINAP: An Efficient Chiral Element for Asymmetric Catalysis. Acc. Chem. Res., 23, 345.

Nozaki, H., S. Moriuti, H. Takaya, and R. Noyori. 1966. Asymmetric Induction in Carbenoid Reaction by Means of a Dissymmetric Copper Chelate. Tetrahedron Lett., 5239.

Ohta, T., H. Takaya, M. Kitamura, K. Nagai, and R. Noyori. 1987. Asymmetric Hydrogenation of Unsaturated Carboxylic Acids Catalyzed by BINAP–Ruthenium(II) Complexes. J. Org. Chem., 52, 3174.

Suzuki, M., H. Doi, M. Björkman, Y. Andersson, B. Långström, Y. Watanabe, and R. Noyori. 1997. Rapid Coupling of Methyl Iodide with Aryltributylstannanes Mediated by Palladium(0) Complexes: A General Protocol for the Synthesis of 11CH3-Labeled PET Tracers. Chem. Eur. J., 12, 2039.

Suzuki, M., H. Doi, K. Kato, B. Långström, M. Björkman, Y. Watanabe, and R. Noyori. 2000a. Rapid Methylation for the Synthesis of a 11C-Labeled Tolylisocarbacyclin Imaging the IP2 Receptor in a Living Human Brain. Tetrahedron, 56, 8263.

Suzuki, M., K. Kato, R. Noyori, Yu Watanabe, H. Takechi, K. Matsumura, B. Långström, and Y. Watanabe. 1996. (15R)-16-m-Tolyl-17,18,19,20-tetranorisocarbacyclin: A Stable Ligand with High Binding Affinity and Selectivity for a Prostacyclin Receptor in the Central Nervous System. Angew. Chem., Int. Ed. Engl., 35, 334.

Suzuki, M., R. Noyori, B. Långström, and Y. Watanabe. 2000b. Molecular Design of Prostaglandin Probes in Brain Research: High, Specific Binding to a Novel Prostacyclin Receptor in the Central Nervous System. Bull. Chem. Soc. Jpn., 73, 1053.

Takaya, H., T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S. Inoue, I. Kasahara, and R. Noyori. 1987. Enantioselective Hydrogenation of Allylic and Homoallylic Alcohols. J. Am. Chem. Soc., 109, 1596.

Takechi, H., K. Matsumura, Yu. Watanabe, K. Kato, R. Noyori, M. Suzuki, and Y. Watanabe. 1996. A Novel Subtype of the Prostacyclin Receptor Expressed in the Central Nervous System. J. Biol. Chem., 271, 5901.

Tani, K., T. Yamagata, S. Otsuka, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, and R. Noyori. 1982. Cationic Rhodium(I) Complex-Catalysed Asymmetric Isomerisation of Allylamines to Optically Active Enamines. J. Chem. Soc., Chem. Commun., 600.

Chapter 5

The Changing Atmosphere in 2004

F. Sherwood Rowland

Introduction

Each breath we take in contains about 21% oxygen (O_2) and a much smaller amount of carbon dioxide (CO_2). The exhaled air has about 16% oxygen (O_2) and 5% carbon dioxide. Green plants, on the other hand, take in air through the stomata and convert the CO_2 into plant matter while emitting gaseous oxygen.

Many other processes also take place with exchange of one gas or another between the atmosphere and lakes, plants, rocks, or the oceans. Although all of these changes are taking place continuously everywhere, the global sum of these exchange processes is not easy to measure. The problem is made more difficult by the fact that the atmosphere is omnipresent, and transparent, except for the clouds. The determination of its molecular composition depended first upon devising an experimental apparatus from which all of the air could be removed, and then devising experimental techniques that could separately identify individual transparent gases introduced into this evacuated space. By 1800, scientists had concluded that the atmosphere consisted mostly of just the two gases nitrogen (N_2) and oxygen (O_2) in the ratio of about 4 parts to 1. The experience of all travelers, that it was equally possible to breathe in distant destinations, together with the experiments of a few scientists, confirmed that the atmosphere was similar everywhere in its main composition, although obviously breathing was harder at higher altitudes.

In 1804, two French scientists–Gay-Lussac and Biot–extended the study of the atmosphere to much higher altitudes by taking an evacuated sphere up in a balloon to an altitude of five kilometers (16,300 feet), and then filling it there. After bringing it back to the laboratory, Gay-Lussac found its composition to be the same 4 to 1 ratio found at the surface, although there was considerably less of both gases at the higher altitude. A few months later, Gay-Lussac, responding to the criticisms of some skeptics, took the balloon up alone, unencumbered by Biot, to seven kilometers (22,700 feet), and analysis of this sample confirmed the ratio of 4 to 1, although with even less of both gases. Our present knowledge two centuries later agrees that the components of the atmosphere mix thoroughly, whether light such as helium or heavy such as CCl_3F (trichlorofluoromethane), to altitudes far above the 50-kilometer top of the stratosphere.

In 1896, the Swedish scientist Arrhenius, realizing that the burning of wood, coal and oil was releasing CO_2 to the atmosphere, calculated that a doubling of its 0.03% composition in air would cause a measurable increase (3°C) to the globally averaged temperature of the Earth. This opened up a discussion that has become pertinent under the headings of global warming and abrupt climate change. As the 20th Century progressed, other studies confirmed that the atmosphere is not a simple mixture of N_2, O_2, CO_2, and water (H_2O) vapor, but contained many additional trace gases. If the sensitivity of measurement extends down to 0.0001% or 10^{-6}, then only nine kinds of molecules are detectable in the nonurban atmosphere–the four listed above, plus methane (CH_4) and four inert gases (argon, helium, neon, and krypton). With a sensitivity of detection carried down to 10^{-8}, five more gases are found–carbon monoxide (CO), hydrogen (H_2), nitrous oxide (N_2O), ozone (O_3), and another inert gas, xenon. All of these gases except the inert ones are involved in biological processes. Another characteristic of all 14 is that they are transparent to visible radiation, which means not only that we cannot see them but also that they are not absorbing any of the visible radiation from the sun. Of course, if they did absorb some green or violet sunlight, the energized molecules would break up quickly, and there soon wouldn't be enough of these molecules left for us to detect.

Much of the interesting chemistry discovered in the past several decades involves additional compounds whose atmospheric concentration never rises above 10-8. The key development then is ever-more sensitive techniques for detecting trace gases, driving the level of successful observation down to 10^{-12} or even 10^{-15}. At these levels, hundreds of different compounds are detectable in the atmosphere even in remote locations.

Ozone at Ground Level

One of the first sets of continuing measurements made in the same location was initiated in the 1870s at Montsouris, near Paris, where the ozone concentration in surface air was analyzed for twenty years. The concentration ratios were about 10 parts per billion by volume (ppbv), with little change from season to season or year to year. The absence of any change between winter and summer certainly suggests that the sun was not then involved in forming ozone near the ground. One hundred years later, similar decade-long experiments carried out at Hohenpeissenberg, near Munich, Germany, showed higher concentrations throughout the year, and approximately twice as much (40 ppbv vs. 20 ppbv) in mid-summer versus winter. The summertime peak indicates that now there is a solar-driven mechanism for forming ozone near the surface.

Recent photographs of central Munich show a brown gaseous layer just above the surface, signalling the presence of the colored molecule nitrogen dioxide (NO_2). This brown color is an identifying marker for high urban ozone concentrations. The

difference between the ozone measurements of the late 19th century and those 100 years later is that we now have many human processes that provide additional gases to the atmosphere. An especially important example involves hydrocarbons and nitric oxide (NO) emitted in automotive traffic, which combines with the aid of sunlight to form additional ozone, an important pollutant in metropolitan smog. These processes in urban environments are becoming more and more prevalent around the globe as the population of the world, and its standard of living, increase.

Increasing Atmospheric Carbon Dioxide

Probably the most significant change in the last 30-50 years for the development of atmospheric chemistry started with the long sequence of carbon dioxide measurements initiated high on the Hawaiian mountain Mauna Loa in 1958 by C.D. Keeling. He also began collecting CO_2 at the South Pole that same year. The detection of changes with time in the amounts of CO_2–or any other gas–in the atmosphere requires a long, well-calibrated series of measurements using a high precision technique. His initial CO_2 measurements in March at Mauna Loa showed about 315 ppmv increasing to about 317 ppmv in May, and then dropping gradually back to 312 ppmv in October, only to rise again toward another peak the next May. This seasonal cycle with a high in May and a low point in October continued year after year.

These changes are caused by the absorption of atmospheric CO_2 for photosynthesis by green plants during the spring and summer growing season, and then its escape into the air from decomposing plant life during the autumn and winter. But the cycle doesn't actually reproduce itself from one year to the next. Rather, each month in the new cycle has slightly higher carbon dioxide concentrations than in the corresponding month the previous year, and the yearly average slowly rises to 325 ppmv in 1970. This long-term rising background is caused by the combustion of fossil fuels–coal, oil and natural gas–for energy production. Keeling has continued to make these measurements for another 34 years, as they moved upward to the present average May concentration of 380 ppmv.

Increasing Sensitivity of Detection from 10^{-6} to 10^{-12}

Keeling's experiments represent one avenue of advance. Carbon dioxide had long been known as an important component of the atmosphere. His major contribution was making measurements of high precision with enough frequency and over a long enough period of time first to isolate the photosynthetic cycle, and then to recognize the monotonic increase underlying it. Another avenue of scientific advance lies in the extension of the instrumental detection sensitivity to lower and lower concentrations.

The British scientist Jim Lovelock invented the "electron capture detector" which increased the instrumental sensitivity for certain molecules–those such as CCl_3F which can "capture" an electron–by a factor of about one million, pushing down well beyond the 10^{-9} level toward 10^{-12} (parts per trillion by volume, pptv).

Lovelock's measurements established that the nearly inert industrial chemical trichlorofluoromethane (CCl_3F–also called CFC, for the chlorofluorocarbon class) was easily detectable in the atmosphere at a concentration of about 50 pptv. Furthermore, Lovelock made measurements on shipboard during a cruise from England to Antarctica that demonstrated that this CFC was present everywhere in both hemispheres. The technological uses for this synthetic molecule were growing rapidly in the early 1970s, and most of these uses involved eventual release to the atmosphere.

Chlorofluorocarbons and Stratospheric Ozone Depletion

This was the point in time that Dr. Mario Molina and I began to consider what would eventually happen to such molecules in the atmosphere. We started initially with three questions one can ask for any compound newly released to the atmosphere: First, does it react with sunlight? The observation of color immediately signals that the molecule has absorbed some visible sunlight because the selective removal of some solar radiation is the process that produces the sensation of color. Molecular chlorine (Cl_2) is a green gas, and breaks up in sunlight in about one hour with the release of two individual Cl atoms. The second question is: does it dissolve in water? Another Cl-containing molecule hydrogen chloride (HCl) is transparent, and doesn't absorb visible solar radiation. However, HCl is water soluble and dissolves in raindrops to form hydrochloric acid, which later rains out in a month or two, removing the chlorine atom from the atmosphere. And finally, the third question: is there a chemical in the air with which it can react? One of the most frequent atmospheric reactants is the atmospheric oxidizing agent hydroxyl radical (HO) which is especially effective with hydrocarbon compounds. Another type of chlorine-containing molecule, methyl chloride (CH_3Cl) , is also attacked by HO that pulls a hydrogen atom from it to form a water molecule, destroying the methyl chloride in the process. This chemical reaction takes about one year on the average.

But CCl_3F and the other CFC molecules are transparent, insoluble in water, and do not react with any atmospheric oxidizing agents. Without any of these tropospheric removal processes, the CFCs can bounce around the atmosphere unchanged for decades.

When Molina and I found that these common removal processes weren't effective, we turned our consideration toward solar radiation other than the visible range to which our eyes respond. We are all comfortable with the visible spectrum displayed by sunlight passing through a prism–red, orange, yellow, green, blue,

indigo, violet. Or in a numerical description, radiation with visible wavelengths stretching from the lower energy red light around 700 nanometers (nm, or 10^{-9} meter) to the higher energy, violet light at 400 nm. The sun also emits invisible light, either less energetic–infrared (IR) or too energetic–ultraviolet (UV) outside the 400-700 nm visible range. The invisible IR radiation acts as a form of heat energy, whereas the UV energy in the 200 nm region is absorbed by molecular oxygen, splitting it into two oxygen atoms. Each of these oxygen atoms then reacts with another O_2 molecule to form the triatomic molecule, ozone (O_3).

Most of these processes occur in the stratosphere between 15 and 40 kilometers altitude, forming an ozone layer that then creates the stratosphere. This is a region in which the temperature rises with increasing altitude, and the necessary heat for this warming is provided by the absorption of additional solar UV by the ozone molecules. The ozone molecules are very good absorbers of UV sunlight, especially at wavelengths shorter than 295 nm, where they are sufficiently successful in capturing this UV light that none of it penetrates to ground level. All humans, and all of the biological species at Earth's surface, are protected against UV radiation below 295 nm because this "ozone shield" in the stratosphere has absorbed it all.

The CCl_3F molecule and the other CFCs are also protected from destruction by this stratospheric ozone, because they are transparent to all solar radiation above 220 nm in wavelength. The only place the CFCs can find such radiation is to aimlessly wander high up into the stratosphere at altitudes of 25 to 30 kilometers with 98% of the atmosphere now below them. There they encounter some 210 nm UV radiation, absorb it, and break apart with the release of a chlorine atom, e.g. $CCl_3F \rightarrow Cl + CCl_2F$. This chemistry then quickly multiplies as the Cl atom attacks ozone to form ClO and O_2, and the ClO reacts with O atoms to form Cl (and O_2) back again. This process is called a chain reaction because the Cl atom is not permanently removed but can repeat the process over and over again–in this case, removing about 100,000 ozone molecules for every Cl atom released! The realization that the technological release to the atmosphere of about 1 million tons of CFCs per year, would be multiplied by 100,000 from the chain reaction, converted what had been for us an isolated but interesting scientific problem into a major global environmental problem–the depletion of the stratospheric ozone layer by chlorofluorocarbon molecules.

Experimental Confirmation in the Stratosphere

Our conclusions in 1974 that the fate of the CFCs lay in UV photolysis in the stratosphere, and was coupled with prospective severe future losses to Earth's protective ozone layer, were all pen-and-paper estimates made by combining the results from several separately known experimental observations. With an annual market value of US$2 billion for the CFCs alone, and perhaps 50-100 times that in

their uses, the demand was quick for experimental confirmation of these calculations in the real atmosphere. The necessary experiment was similar to that carried out by Gay-Lussac 170 years earlier–transport evacuated spherical containers up on a balloon, open them at the desired altitudes in the 20-35 kilometer range, and return them to Earth for analysis in the laboratory. Two research groups, each based in Boulder, Colorado, carried out such experiments in 1975. Because the altitude target for the balloon was much higher than Gay-Lussac's 7 kilometers, the balloon was unmanned and was equipped with pressure-triggered devices set to open the spheres at a number of different altitudes. The experimental measurements agreed very well with our calculations made a year earlier, confirming that (1) the CCl_3F molecule, even though it is about five times as heavy as air, did reach the stratosphere; and (2) the CFC molecules decomposed at the altitudes predicted for the photochemical process.

Long Atmospheric Lifetimes for the CFCs

The next step in confirmation of our calculations required measurements of the amounts of the CFC molecules in the global atmosphere, and this in turn meant obtaining surface-level air samples from a variety of latitudes in the northern and southern hemispheres, and returning them to our laboratory for analysis. We started out with collections from the West Indies, the U.S. west coast up to Alaska, and from South America. Later we transferred the southern hemisphere collections to New Zealand and other Pacific islands. Our air sample collections in 1979 showed CCl_3F concentrations in both northern and southern hemispheres more than double the amounts found in 1971 by Lovelock. Similar results were found by several other research groups, and this increase in global concentration confirmed that these molecules have very long atmospheric lifetimes. The best current estimates are lifetimes of 45 years for CCl_3F and for the companion molecule CCl_2F_2 about 100 years. After these molecules are released into the atmosphere, its natural cleansing actions require many decades to remove the CFCs.

Increasing Methane Concentrations in the Atmosphere

My research group needed only a small fraction of the air trapped in these canisters for the measurements on the CFCs, so we used some of the remaining air for accurate assays of the amount of methane in the atmosphere. Although methane had been suspected as a sometime component of air through much of the 19th century, its presence in air in remote locations was only established in 1948. In our first methane assays in 1978, we found about 1.6 ppmv in the northern hemisphere and 1.5 ppmv in the southern. Then when we collected another set of canisters during the next year,

we found slightly more methane in both hemispheres– another atmospheric gas whose concentrations were increasing.

The sources of methane are quite varied and many of them are under the control of mankind such as the emission from rice paddies during the flooded seasons, with the methane actually travelling up through the plant stems rather than as bubbles rising in the water. Cows are another important source. With each cow emitting about 200 grams per day, multiplied by 1.6 billion of them worldwide, the cumulative amount is significant on a global basis. We have continued these global assays for methane every three months since the late 1970s, and have watched the global amount rise from 1.52 ppmv to the present 1.78 ppmv. Any molecule with more than two atoms is complex enough to be a potential greenhouse gas, and over the past century methane has been the second most important after Keeling's CO_2.

The Greenhouse Effect

About half of the solar energy entering into Earth's atmosphere comes in the visible wavelengths with an equal amount in the nearby IR regions and a few percent of the energy arriving as UV light. This incoming energy needs to be matched by an equal amount of outgoing energy, or the Earth's temperature would quickly change. (When we talk about the long-term effects of greenhouse gases, temperature changes of perhaps one degree Celsius over 25 years are mentioned, which corresponds to an increase of about 0.0001°C per day–so the incoming and outgoing energies are almost completely balanced daily.) Although the total amounts of energy in and out are closely matched, the wavelength regions for solar emission and terrestrial emission are quite different because these are determined by the surface temperature of the emitting bodies–about 5800 degrees Kelvin for the sun, and 287 degrees K for the Earth–the sun's surface is about 20 times as hot as Earth's. The peak in the incoming solar irradiation lies approximately at 500 nm wavelength (yellow light), whereas the outgoing terrestrial radiation is around 20 times longer in wavelength, peaking near 10,000 nm, or in the usual terminology, a wavelength of 10 microns, in the "far infrared."

A very straightforward calculation can be made of the temperature needed for the Earth to emit an amount of energy equivalent to that coming in from the sun, with only two additional bits of data–the distance of the Earth from the Sun and Earth's albedo, the fraction (0.30) of solar energy reflected directly back to space, plus the assumption that all of the far infrared radiation emitted by the Earth goes directly into outer space. When this calculation is performed for the planet Mars, the estimated surface temperature is in good agreement with the observed temperatures–almost all of the far infrared radiation does make it into space through the very thin Martian atmosphere. On the other hand, when the parameters for Earth are entered into the equation, the expected temperature comes out as 255 degrees Kelvin (-18° Celsius),

32 Celsius degrees less than the 287 K (+14°C) actually observed. This discrepancy is the natural greenhouse effect, which was present in the years 1900 and 1800, and long before that as well.

The modern version of the greenhouse effect discussion is not whether there is a natural greenhouse effect, because there is, and everyone agrees that there is. Rather they are the questions of whether carbon dioxide and methane and other gases added during the 20th century have already increased the greenhouse effect from 32°C to 33°C, and whether their continued release during the 21st century will result in a global average greenhouse effect of 35°C or perhaps 37°C by 2100. An important related point is that the reality of this natural greenhouse effect is not debated–all of the scientific community agrees that the evaluation has been done correctly. And no one has provided an alternative explanation for its cause other than through the greenhouse gas concentrations in the atmosphere.

Greenhouse Gas Absorption Spectra in the Far Infrared

The explanation for the natural greenhouse effect is the failure of the assumption that all of the far infrared radiation emitted by Earth escapes to space. It doesn't, and the reason is that the greenhouse gases selectively absorb some of these terrestrial emissions. And Earth has to warm up to produce enough additional far infrared radiation to make up for that absorbed by the greenhouse gases. For each of the greenhouse gases–carbon dioxide, methane, nitrous oxide, CFCs, etc.–there exists a particular pattern in the far IR region of transparent wavelengths and strongly absorbed wavelengths, and the pattern for the atmosphere as a whole is the sum of these individual absorption patterns. The evidence that this absorption actually occurs in Earth's atmosphere is readily obtained with an infrared spectrometer on an orbiting satellite looking down at the Earth beneath. Such satellites record the outward transmission of terrestrial IR radiation in the absorptive and transparent wavelength patterns in the far infrared. When the satellite is over the Sahara desert, the emissions in the transparent far-IR regions correspond to a surface temperature of 47°C, the temperature of the sand below.

However, in the major wavelength region absorbed by carbon dioxide, far less radiation makes it into space and the observing satellite, because it has been removed by interaction with the carbon dioxide molecules in the atmosphere. An hour later when the satellite is looking down at the high Antarctic plateau, the transparent region detects emissions corresponding to -25°C or colder, while the carbon dioxide absorption region registers even less radiation than expected for this much lower temperature. These satellites confirm the reality of the absorption of terrestrial infrared emissions, the basis of the greenhouse effect.

Positive Feedbacks in Global Warming

Once the Earth begins to warm from increased IR absorption by increased greenhouse gas concentrations, there are some positive feedbacks that tend to amplify the warming. In the Arctic Ocean, interfaces exist in which liquid water and floating ice are in contact. As warming occurs, some of the surface ice melts and becomes liquid water. The reflectivities of ice and water are very different: ice reflects most of the solar radiation that strikes it, whereas water absorbs most of it. The melting of ice causes a highly reflective surface to be replaced by an absorbing one, so that even more heat is retained at the surface, contributing to further warming. The same effect is attained at snow-rock interfaces on land–snow reflects sunlight, rocks absorb it. When the snow melts, much more heat is retained by the rocks, and additional surface warming occurs

There are many signs in the North Pole region now of disappearing snow and ice, and rising temperatures. The Arctic Ocean especially has large areas with water and ice in direct contact. This feedback is not as strong in the South Pole region because Antarctica is predominantly a continent, land covered with three kilometers of ice, and with considerably lower temperatures than the 0°C that marks the coexistence of floating ice and cold water.

The Ice Ages

Early in the 19th century geologists were puzzled by their observation in the European Alps of very large boulders that seemed totally out of place in their surroundings–totally different composition and appearance, often resembling other geologic sites many kilometers away at higher altitudes. Enough of these strangers were found that they were described as a class of out-of-place objects known as the "erratics." Over the last part of that century, the scientific world became convinced that these boulders had been entrapped in glaciers that had transported them down the mountains, and then, when the glaciers disappeared during warmer conditions, left them stranded in these Alpine valleys. This was the beginning of the present understanding that thousands of years ago the Earth had a much colder climate–an Ice Age, one of a long series extending back one million years or more. At the coldest part of the most recent Ice Age 21,000 years ago, all of Scandinavia, all of Canada, and large parts of northern Europe plus New England and the Great Lakes region of the United States were covered by ice two to three kilometers deep. With all of that water frozen and piled up on the land, the oceans were about 130 meters shallower than at present–Alaska and Siberia were connected by a broad land bridge, England was not an island, and the Black Sea was an inland lake, among many other altered topographic differences from the present.

Glaciers still exist, especially in Greenland, Antarctica, the Alps, the Canadian Rocky Mountains, and many high altitude tropical locations. At the Quelccaya glacier in the Peruvian Andes, the predominant wind directions have a strong alternation every year between moisture-laden winds from the Amazon, and very dry, dusty ones from the Bolivian altiplano and northern Chile. The result as one digs down into the glacial ice is a readily visible yearly alternation between ice and dust layers that allows counting back in time for a thousand years or more. In Greenland and Antarctica, the temperature alternation between summer and winter is preserved in the isotopic composition of the water molecules, with changes in the ratios of both $^{18}O/^{16}O$ and 2H/1H with the outside temperature variations. Moreover, the initial mixture of snow and ice from a storm has large amounts of air mixed in with the frozen water. Gradually as the years pass and more and more ice accumulates creating strong pressures on the buried layers, much of this air is squeezed out. Eventually, as the ice accumulates to a depth of 50 meters or more, no additional air is driven out, and about ten percent of the ice volume is trapped in ice bubbles no longer connected with one another. Inside these individual bubbles is ancient air, with the molecular composition of bygone eras.

Atmospheric Composition in Ice Core Bubbles

Measurements in ice cores drilled down out of glaciers from regions with very heavy snowfall have concentrations of greenhouse gases such as carbon dioxide, methane and nitrous oxide that show that each of these gases had nearly a constant composition for the last 10,000 years. This period ended only relatively recently, about 200 years ago, when all three of them began to increase in concentration, as demonstrated by analysis of the more recently trapped bubbles. The carbon dioxide concentrations in these ice cores were about 280 ppmv until around 1800, when a slow rise began, reaching, as we know from Keeling's data, 315 ppmv in 1958 and about 377 ppmv in 2004. The increase in carbon dioxide concentration in the atmosphere, of course, corresponds to the exponential expansion in the burning of coal and oil for energy since the Industrial Revolution. The methane concentrations in the air bubbles were about 700 ppbv prior to 1750-1800, and then began to rise rapidly toward the present 1780 ppbv. At the highest point of Greenland, known as Summit, and at Vostok, 1300 kilometers from the South Pole, ice cores have been drilled several kilometers down, toward air bubbles that were trapped up to 700,000 years ago. During the past 420,000 years, the trapped gases exhibit a series of four ice ages, each separated from the others by an interim warmer period. The air bubbles trapped during the 10,000 years preceding the present 10,000 year period of stable, warm temperatures, show very sharp drops in temperature and in the trapped concentrations of carbon dioxide, methane, and nitrous oxide because the period from about 20,000 years ago to 10,000 years ago represented global emergence from the last great Ice Age. Throughout the 400,000-year ebb and flow of the Ice Age

temperatures, the amounts of carbon dioxide varied from about 190 ppmv in the coldest periods to 280 ppmv in the warm interglacial periods for more than 400,000 years–until the substantially greater rise in carbon dioxide concentration took over during the last 200 years. In close parallel, methane concentrations varied from about 300 ppbv in the coldest eras and 700 ppbv in the warm periods–until more than doubling during the past 200 years.

We are now living in a period in which the concentrations of greenhouse gases such as carbon dioxide and methane have moved into levels much higher than the Earth has experienced for the past 400 millennia. And the causes of these elevated greenhouse gas concentrations are mostly the consequence of the various activities of mankind.

Smog and Urban Pollution

As is true of many cities, a startling contrast exists between photographs of Santiago, Chile, on clear, unpolluted days, and on the much more frequent, visually impaired, smoggy days. Smog comes from two major types of atmospheric pollutant: particulate emissions, and gaseous pollutants, and both of these are often the consequence of automotive traffic. A major gaseous pollutant is ozone formed by the simultaneous presence of unburned hydrocarbons (or carbon monoxide) coupled with nitrogen oxides, with sunlight added to the mix. Our research group has been studying the hydrocarbon precursors to the formation of urban ozone in many cities around the world, including Santiago, Chile. Our standard method relies on the collection of a series of air samples in two-liter stainless steel canisters, transporting them back to the home laboratory, and carrying out analysis of both the qualitative presence and the quantitative amounts of about 200 different chemical compounds.

Our ability to detect components at the 10-12 level is sufficiently sensitive that measurable amounts of most of these chemicals are found in the urban atmosphere of almost every city. Typically, we find substantial quantities of hydrocarbons such as methane, propane, butane, hexane, benzene, toluene, and nearly 100 others; the well-studied CFCs CCl_3F, CCl_2F_2, and CCl_2FCClF_2 and many other chlorine and bromine compounds; some sulfur compounds; and lesser-known compounds as well such as the alkyl nitrates (e.g. butyl nitrate, $C_4H_9ONO_2$). The latter is a marker compound, created as a minor side product from the formation of urban ozone from the molecules butane (C_4H_{10}) and nitrogen dioxide (NO_2). When we measure butyl nitrate, we know that the butane pollutant has simultaneously formed much larger amounts of ozone through its major reaction path.

In our study of pollution in Santiago, we were aided by 25 students from a local university, who were stationed all over the city in the early morning and filled an air canister at 5 a.m. They then returned to the same locations with other canisters that were filled at 9 a.m. Comparison of the 5 a.m. and 9 a.m. pollution patterns around the city readily distinguished which pollutants were traffic-related, and which were

not. Substantial concentration increases were found during this period for carbon monoxide and other compounds long associated with emissions from automotive traffic. On the other hand, propane (C_3H_8) was identified in approximately equal quantities at both 5 a.m. and 9 a.m., indicating that its presence was not enhanced by the morning rush hour traffic. Instead, propane and butane are important components of liquefied natural gas, used extensively in Santiago for household heating and cooking, and stored in containers that are often not leak-tight. Such urban measurements can provide information useful for smog-reduction efforts in each city. Mexico City also makes widespread use of liquefied natural gas, and identification of the importance of its leakage allowed alleviation of some of the worst smog contributions by removal of the highly reactive butenes from the composition.

Global Population Growth

Although urban pollution has been known for about 800 years, the size of cities and the magnitude of their pollution have increased greatly during the 20th century. The global population grew from 1.6 billion people in 1900 to 6.1 billion in 2000. London was the largest city in the world in 1900 with 4.5 million inhabitants; it doubled in size by 2000, but was now the 20th largest city globally. The contiguous cities Tokyo/Yokohama led the 2000 list with a population of 29 million people by one estimate, and Cairo was 15th. Only 13 cities were on the 1900 list with populations of 1 million or more; now there are more than 350 cities over 1 million, with new additions almost monthly. Most of those cities are also rapidly expanding their automotive traffic, and are suffering from its accompanying smog problems.

Los Angeles ran into serious smog problems in the 1950s and soon began introducing various kinds of regulatory controls. The progress made in cleaning up the air in Los Angeles can be assessed from the official figures for 1965 to the present on the number of days with violations at three progressively worse ozone levels: 95,200, and 350 parts per billion. In the 1960s Los Angeles violated the 350 ppb standard on 50 or 60 days per year, but the last day with ozone levels higher than 350 ppb occurred in 1982, more than 20 years ago. The last violations of the 200 ppb standard have been one each in 1998 and 2003, down from more than 100 per year in the 1960s. And the number of days in violation of the 95 ppb standard has dropped from about 300 per year in the 1960s to 70 or 80 now. Clearly, regulatory actions can help greatly in reducing urban pollution events, but the Los Angeles situation with regulatory actions that began 50 years ago still leaves much room for improvement, with violations of the 95 ppb standard now still found during 20% of the days. There, as in most cities, the impetus for regulation usually doesn't become strong until the local situation is quite bad–often from some pollution episode with serious health problems, sometimes including multiple fatalities. In perhaps the most famous example, London's heavy, black fogs were not controlled until after a disastrous several-day event in 1952.

Aircraft Experiments and Biomass Burning

Many of the chemical reactions involved in urban smog can also be observed in biomass burning, the clearing of forests, or the burning of agricultural waste. Satellite observations of the Earth after dark show the bright lights of cities every night that clouds do not obscure, and there are a few other regular nonurban light sources such as the flaring of natural gas in the North Sea. The same satellite observations also reveal thousands of lighted areas which last only a week or two, and these are biomass burning locations in Africa, South America, Australia, and elsewhere.

An important mechanism for investigating the current state of Earth's atmosphere has been the creation of large teams of atmospheric scientists to participate in 3-month-long, aircraft-based, simultaneous studies of regional conditions throughout the world. The overlap in time and location is an important aspect because of the large amount of simultaneous background data that becomes available, and is often useful in understanding the whole picture of the particular atmospheric condition being explored. Our research group has been part of 15 such investigations globally since 1988, many of them in the 20-year long NASA-supported GTE (Global Tropospheric Experiment) series. GTE missions in the past decade have often employed two large aircraft, one of them a completely rebuilt DC-8 of commercial origin. Both aircraft are configured for our research with a collecting tube extending beyond the fuselage through which outside air can be pumped in to an array of more than one hundred of our usual air canisters.

On one occasion during the 1996 GTE mission in the tropical South Pacific, the DC-8 took off from Fiji and headed on its way toward its destination in Tahiti. On the initial climb out, the laser instruments operated by another research group on the airplane indicated between altitudes of about 2-4 kilometers a plume of air with an unusually high ozone content–at its highest, exceeding the 95 ppb level applicable to Los Angeles. The DC-8 then leveled off at 10 kilometers, and for more than an hour the laser data continued to track the high-ozone plume below. The DC-8 then changed altitude down to one kilometer, a routine pattern change on research flights, passing through the high ozone plume on the way. Our group filled numerous canisters during the descent, and later analysis showed much higher concentrations of numerous hydrocarbons at the plume altitudes than found either above or below. Although some such plumes in theory might originate over the ocean or from isolated islands, our experience is that those we have encountered all have origins in biomass burning in distant continental areas.

An entirely separate system of atmospheric experimentation releases radiosondes–balloons equipped to relay back information about their location–every six hours over most of the world, which are then followed from below to determine from their motions the wind directions and speeds at all flight altitudes. This system is primarily for the use of commercial aircraft in planning flight routes, but the data are not discarded after the route-planning value has passed. Instead these same wind data are stored and can be used months or years later for the calculation of back-trajectories–the path followed by each particular air parcel for the 15 or 20 days prior

to its encounter with the aircraft. On this descent, the calculated tracks for the air parcels at altitudes above and below the ozone plume had been over the open Pacific Ocean for more than two weeks. The plume air parcels, however, all tracked back over Australia three or four days earlier, and eventually southern Africa 9-10 days prior to arrival near Fiji. Either Australia or Africa were the logical sources for the biomass burning ozone-formation precursors that had created the plume.

Analysis of the composition of all of these canisters disclosed which hydrocarbons and other compounds were elevated in the plume in comparison to those found above and below. Equally important, the chemical analyses also disclosed which compounds were not elevated, including some which were well-known to be formed in biomass burning. These compounds were certainly formed, but reacted too rapidly in the atmosphere to survive until their capture by the DC-8 a few days later. For either an African or an Australian burning source, the plume southeast of Fiji indicates that air parcels carrying pollution can travel many thousands of miles with relatively little dispersal. Our analysis indicated that this plume was more than a week old, and originated in southern Africa.

Such long distance spread of pollution is also observed in the northern hemisphere. With prevailing west-to-east winds, regional pollution from the eastern U.S. can reach Europe, European pollution carries to Asia, Asian pollution can cross the Pacific to North America. In effect, the north temperate zone becomes a merged band of ozone pollution stretching around the world between about 25°N and 55°N latitudes. The consequence is that local pollution is not actually confined to its immediate vicinity but becomes regional and eventually global in its effects.

The Antarctic Ozone Hole

The CFC-stratospheric ozone depletion situation was described earlier. Many countries of the world collectively agreed in the early 1950s to an International Geophysical Year (IGY) later in the decade, during which all would conduct a wide variety of year-long geophysical experiments in the same time period, so that data would overlap for comparison purposes. The IGY eventually was conducted over an 18-month period from July 1957 through December 1958. The additional six months allowed for year-long studies even in the polar regions where favorable conditions for logistical access are six months apart in the north and the south. Keeling's measurements of global carbon dioxide in Hawaii and at the South Pole were initiated during the IGY, but fortunately were transformed into permanent installations.

The first experimental stations set up to measure the amount of ozone overhead were established in the 1920s, and the longest record is from Arosa, Switzerland, with near-daily measurements since 1931. During the IGY the British Antarctic Survey (BAS) was established and began ozone measurements at Halley Bay on the Antarctic Coast. Because the standard ozone measuring device depends for normal

use on direct observation of solar UV light, the Halley Bay data cover the months from October through March, the sunlit months in Antarctica.

During October 1957, and succeeding Octobers for about 15 additional years, the average recorded ozone at Halley Bay was about 300 Dobson Units (DU). One Dobson Unit represents approximately one part in 109 of the molecules in the atmosphere, and 300 DU is also approximately the average total ozone for the entire world.

However, in the late 1970s the October ozone average measured over Halley Bay began to decrease, and by 1984 the average had fallen below the 200 DU mark–values lower than ever previously observed anywhere in the world. The published B.A.S. report of this decline in 1985 attributed the likely cause to effects from chlorine reactions associated with CFC accumulations in the atmosphere. This severe drop in Antarctic ozone was quickly confirmed by NASA's Total Ozone Monitoring Spectrometer (TOMS) on the Nimbus-7 satellite launched in late 1978. The TOMS instrument provided full global coverage with more than 100,000 measurements of ozone each day in both the northern and southern hemispheres, beginning in November 1978. In early October 1979, the TOMS instrument recorded minimum ozone values of about 250 DU over a wide area of Antarctica, falling to 170 DU in 1983 and 120 DU in 1987. The graphic color display of this Southern Hemisphere ozone data led to its description as the "Antarctic Ozone Hole," and that term has been used ever since.

After the first public announcement of the Halley Bay data, a ground-based expedition was quickly organized to go to McMurdo, Antarctica, in August 1986, and again in 1987, plus a second expedition in 1987 utilizing the NASA DC-8 aircraft and its very high-altitude ER-2 for flights over Antarctica . The ER-2 carried instruments that separately measured ozone and chlorine oxide (ClO), with the latter viewed as a marker for the importance of atomic chlorine–and chain reactions–in the removal of ozone. On August 23 the first successful ER-2 flight from its base in Punta Arenas, Chile, showed very high concentrations of chlorine oxide as the aircraft flew over Antarctica at an altitude of 18 kilometers, but little change in ozone. However, this was late winter, and sunlight was just returning to Antarctica after the long winter darkness. By September 16, the ER-2 flight showed chlorine oxide was again very high, and now about two-thirds of the ozone had disappeared during that three-week interval.

The Montreal Protocol to Control CFC Emissions

The ground-based expedition to McMurdo in 1986 had indicated a chemical explanation for this ozone loss, and the accumulated data from both ground and airborne expeditions in 1987 clearly pointed toward chlorine from the CFCs as the major culprit behind the Ozone Hole. These data also convinced the major nations of

the world to support the Montreal Protocol of the United Nations, which in late 1987 called initially for a reduction in CFC production by 50% effective in 1999. In London in 1990 this was raised to a full production ban, and in 1992 in Copenhagen the effective date was moved up to January 1996. The less affluent nations, which had always produced and used very small amounts of these compounds, were given a deadline delay of ten years. Ongoing current measurements in the lower atmosphere confirm that the Montreal Protocol is working well, with the total organic chlorine content–the precursors for stratospheric ozone depletion–actually decreasing slowly from a maximum in 1994–even faster than required by the Protocol. However, a time delay of 5-10 years exists between the tropospheric concentrations and the full effect on reduction of ozone loss in the stratosphere. The many decades-long atmospheric lifetimes of the CFCs ensure that full recovery of the stratospheric ozone layer will also stretch out toward the end of the 21st century.

Global Warming and Climate Change

I will review some aspects of the greenhouse effect and the climatic changes expected in the future. In the present industrial world, the energy sources are, in order of importance, oil, coal, natural gas, hydro, and nuclear power. About 85% of this energy arises from the combustion of the three carbon-based fossil fuels, and the end product of each is carbon dioxide released to the atmosphere. If we examine the geographical sources of this carbon dioxide over the past 50 years, roughly one-fourth each came from the United States, the Soviet Union, and its successors, the rest of the OECD countries, and from the developing countries especially China and India. In 2000 approximately 6 billion tons of carbon was released to the atmosphere in the form of 20 billion tons of carbon dioxide. The population of the world in 2000 was also approximately 6 billion, making the per capita emission about one ton of carbon per person. The largest national emission per capita was from the United States, with 5 tons per person per year. Australia and Canada were close behind with more than 4 tons per person per year. France, with all of its electricity provided from nuclear energy, needed only about 2 tons/year/person. Countries such as India and Nigeria had emissions of less than 0.2 ton/year/person. The intensity of energy usage is closely related to the affluence of the different societies, with the exception of those that chose to go heavily nuclear, or have access to plentiful hydro power. Any attempt to control carbon dioxide emissions requires solving the problems associated with future growth and development in all countries, because of the close relationships among carbon dioxide emissions, energy use, and improved standards of living.

Modeling of the future consequences of continued growth in the concentrations of greenhouse gases leads to estimates of a global temperature increase by 2100 from 1.5°C to 5.4°C. As discussed earlier, this increase will not be expected to occur uniformly over the globe, but will probably rise at double this global average

temperature rise in the high latitudes of the northern hemisphere, which are already showing many signs of a thawing world. Such temperature changes will then be expressed in other physical and biological effects, often quite regional in nature. For example, the Kenai peninsula in Alaska has already suffered the destruction of about 6,000 square miles of contiguous spruce forest, attributed to warmer winter temperatures that allowed much larger survival of its nemesis, the spruce bark beetle. The beetle was already there, and usually was strongly suppressed by the winter cold. When the typical winter-kill failed, the beetle multiplied and destroyed the forest.

A more global result will involve rising sea levels with two factors to consider. The first is the warming of the oceans, which causes water to expand. The second is the melting of landlocked ice, most of which lies over bedrock in Greenland and Antarctica. The current estimate is as much as 1 meter sea level rise by 2100, which would have very strong effects in the Nile delta surrounding Alexandria, in Louisiana around New Orleans, and for many low-lying island nations such as the Maldives in the Indian Ocean. And high-altitude glaciers are melting all over the tropics–such as the Quelccaya glacier in Peru mentioned earlier–as well as in the temperate mountain zones.

The recent Intergovernmental Panel on Climate Change report issued in 2001 concluded that the global temperature had risen 0.6°C over the past 100 years, with much of this increase coming in the past 20 years. Thermometers have been distributed widely enough for valid measurements of global average temperatures only since about 1860, and the ten warmest years in that 140-year record have all been recorded since 1990. In the past, the energy output of the sun has varied somewhat, and may have contributed to the "Little Ice Age" experienced by Europe 200 years ago. However, orbiting satellites have measured the energy output of the sun over the past 25 years, and have demonstrated that solar energy variations have not been the cause of the rapid recent global temperature increase.

Conclusion

The Earth is in a period of rapid increase in global temperature for which by far the most likely explanation is the increasing atmospheric concentrations of greenhouse gases, mostly as the consequence of the many activities of humans. The full climatic consequences of a "business as usual" approach to the accelerating emissions of greenhouse gases cannot be definitively estimated now. At the present time, the chief approach toward regulation of carbon dioxide emissions is through the Kyoto Protocol, which at best would only reduce the global growth rate of those emissions by a few percentage points. For many countries, including the United States, the emission rates of carbon dioxide continue to rise, and any substantial regulatory action toward greenhouse gas emissions lies in the uncertain future.

Selected References

Alley, R.B. 2000. The Two Mile Time Machine. Ice Cores, Abrupt Climate Change, and our Future. Princeton University Press. 229 pages.

Benedick, R. 1998. Ozone Diplomacy, New Directions in Safeguarding the Planet. Harvard University Press. 446 pages.

Brimblecombe, P. 1987. The Big Smoke, A History of Air Pollution in London Since Medieval Times. Methuen, London. 185 pages.

Christianson, G. 1999. Greenhouse, The 200 Year Story of Global Warming. Walker & Co., N.Y. 305 pages.

Davis, D.L. 2002. When Smoke Ran Like Water, Tales of Environmental Deception and the Battle Against Pollution. Basic Books, N.Y. 312 pages.

Dotto, L., and H. Schiff. 1978. The Ozone War, The Controversy among Scientists, government and big business over our Precious Ozone Layer. Doubleday, N.Y. 342 pages.

Fagan, B. 2000. The Little Ice Age, How Climate Made History 1300-1850. Basic Books, N.Y. 246 pages.

Fagan, B. 2004. The Long Summer, How Climate Changed Civilization. Basic Books, N.Y. 284 pages.

Finlayson-Pitts, B., and J.N. Pitts, Jr. 1999. Chemistry of the Upper and Lower Atmosphere. Academic Press, San Diego. 969 pages.

Gelbspan, Ross. 1997. The Heat is On. Addison Wesley Publishing, N.Y. 278 pages.

Gelbspan, Ross. 2004. Boiling Point. Basic Books, New York. 254 pages.

Houghton, John. 2004. Global Warming, The Complete Briefing, 3rd Edition. Cambridge University Press. 351 pages.

IPPC Report. 2001. Climate Change 2001. Third Assessment Report of the Intergovernmental Panel on Climate Change. Synthesis Report. Cambridge University Press. 397 pages.

Nance, J.J. 1991. What Goes Up, The Global Assault on our Atmosphere. William Morrow Co., N.Y. 324 pages.

Roan, S.L. 1990. Ozone Crisis, The 15-Year Evolution of a Global Crisis. John Wiley, N.Y. 270 pages.

Scientific Assessment of Ozone Depletion: 2002. Global Ozone Research and Monitoring Project–Report #47. 2003. World Meteorological Organization. Geneva. 498 pages.

Seinfeld, J.H., and S.N. Pandis. 1998. Atmospheric Chemistry and Physics, From Air Pollution to Climate Change. John Wiley, N.Y. 1326 pages.

Wayne, R.P. 2000. Chemistry of Atmospheres, 3rd Edition. Oxford University Press. 806 pages.

Weart, S.R. 2003. The Discovery of Global Warming. Harvard University Press, Cambridge. 228 pages.

Section 2

Overview

Chapter 6

The Getting of Wisdom: The Meaning of the New Life Sciences

I. Serageldin and G.J. Persley

Introduction

Today, we live in a world where all our lives are increasingly affected by science. Globalization and the relentless movement toward the knowledge-based societies of tomorrow brings the promise of longer, healthier, more fulfilling lives, but also the perils of greater inequities. There is real danger that the benefits of proprietary science will serve to bring more and more to the privileged few, rather than serve the needs of the billions of the marginalized poor and their children. The developing countries also will not be able to adjust fast enough to the needs of the competitive global economy of science-based production and knowledge-based income.

Today, a revolution is taking place in the biological sciences. It is fueled by the ground-breaking work in molecular genetics, the enormous advances in informatics and computing and the enormous sums being invested in research in the North. Now, the benefits of this revolution must be harnessed in the interests of humanity, for the poor, and for the environment.

Today, we are living in a time of unmatched opportunities. We can dream of new scientific breakthroughs and new products that can help humanity as never before: New higher yielding plants that are more environmentally friendly, new remedies for killer diseases, edible vaccines, single cell proteins to feed cattle and clean wastes, hyperaccumulating plants to take toxins out of the soil, expanding forests, and habitats where more species will thrive and so much more.

Today, we can dream of a future of sustainable development where humans thrive in harmony with each other and with the environment. But there is no guarantee that the products of the new breakthroughs of science will not transgress against nature and deeply held ethical views. Or that they will not exacerbate poverty even as they hold the keys to its reduction.

Today is indeed an exhilarating time for the biological sciences, similar to what physics experienced in the glorious forty years between 1905 and 1945, when all the concepts were changed…from cosmology to quantum physics…from relativity to

the structure of the atom.

Today, we are decoding the very blueprints of life. We are learning the deployment and expression of genes and like physics in the first half of the last century, we are confronted by profound ethical and safety issues, complicated by new issues of proprietary science.

Ethics, Patents, and the Poor

BioVision Alexandria 2004 brought together a wide variety of scientists to explore the social, economic, and ethical concerns surrounding the new life sciences, under the broad theme of "Ethics, Patents and the Poor." The economic context of the new life sciences includes the income divide, the science and technology divide, and the digital divide.

There are differing issues surrounding the acceptance of new technologies in medicine, industry, agriculture, and the environment. Public-private partnerships (PPPs) need to be looked at in the context of another three Ps: patents, price, and poverty. Intellectual property rights continue to be a major issue of concern, particularly in developing countries. What is needed is innovative property regimes to mobilize both private investments in science and technology, and in public goods.

The social/ethical context of life sciences includes public perceptions, trends, and trust, all of which are critical. The risks and benefits in all new technologies–green, gene, and evergreen–must be studied and assessed. To do this effectively, strategies must be developed for risk assessment and risk management.

In relation to agriculture, biodiversity, and the environment, an "evergreen revolution," as articulated by M.S. Swaminathan and others, would lead to productivity in perpetuity, and be based on principles of ecology, economics, and social and gender equity. There are threats to the evergreen revolution in agriculture, including biotic and abiotic stresses (drought, salinity), climate change effects (sea level rises, higher temperatures), and market factors that need to be resolved if this dream is to become reality.

The benefits from an evergreen biosciences revolution are many: For example, future rice varieties will be more productive, nutritious, have medicinal qualities, more diversity, and produce valuable by-products. The rice genome is yielding valuable information to help resolve some of the threats to sustainable rice cultivation for the next millennia.

BioVision Alexandria 2004 was not only a celebration of science, but also a celebration of partnerships, founded in a sense of common humanity. We recognize the inequalities at the start, and promote capacity building throughout the world. We also recognize that this requires action in the developing countries as well as an outstretched hand from the industrial North. We must act on policy, on human resource development, on institutions and autonomy, on recognizing the balance between the public and the private, and their complementarity, and on finding appropriate financing mechanisms.

Challenge in Food and Agriculture

Many biotechnological applications provide benefits to sustainable and/or organic agriculture–in areas such as soil fertility, water quality, plant and animal health, postharvest food quality, and the environment. Transgenic technology is generally unacceptable to most organic growers, and is not a market-certified technology for most organic agriculture. It is important, however, that consumers have a choice. These issues are of great concern, and must be addressed through engagement of civil society in science and ethical discourse.

Partnerships from discovery to delivery

The key to a successful partnership is to identify a major opportunity or problem to address, then identify partners that can contribute toward a solution, and who can benefit from the partnership. It is essential to map out the discovery to delivery chain. Another key to success is early involvement and communication with stakeholders. This means "no surprises" later in the process. Regulatory and trade issues need to be addressed, as well as plant breeding and seed production systems for delivery. Effective partnerships are those that deliver new knowledge, new approaches, and benefits to the participants and to society.

Banks with a difference

Community stakeholders should be aware of the numerous "banks" involved in a successful partnership. These include gene banks–field gene banks, seed banks (in situ on-farm conservation, ex situ on-farm conservation, botanical and zoological gardens), water banks, and grain banks. They also include "biosphere trusts," which pay attention to conservation, enhancement, sustainable use, and equitable benefit sharing in a specific biosphere. Examples include partnerships between indigenous people and scientists. Participatory plant breeding involves communities and science partners, gives access to genetic resources, and enables access to benefits by farmers.

Common elements of successful partnerships

The partnerships share common objectives, and a clear focus. They involve people more than institutions, there are shared rewards, and reinvestment is required. There is also a need for constant communication, transparency, and time and space are required. Some questions arise: Why are there not more successful partnerships? What are the risks? Who is responsible for liabilities? Is there a strong fear of failure? Can successes be cloned?

Partnerships need clear objectives, and a determined focus to bring products to people and markets. Intellectual property will be generated in the process, and will need to be managed. There will be a need for a constant flow of accurate and timely information.

The purpose of development-related partnerships is to provide better livelihoods for poor people, by improved management of natural resources, and better stewardship of the environment. There are many rewards from working together toward an agreed outcome. Clear recognition of the role of women in agriculture and other sectors is essential. Faith and local beliefs and customs play an important role as well in developing and maintaining successful partnerships.

Challenges in Health Alliances

In addressing human health, there are an increasing number of health alliances, for example on HIV/AIDS, malaria, TB, and access to vaccines for orphan diseases. These alliances are based on ethical principles, take a multidisciplinary approach, involve members of the community, and public/private partners. Sustainable funding and capacity building are essential to success. These alliances differ in some respects, but they do share the common objective of mobilizing human, financial and scientific resources to address human diseases. They can also influence health systems through patient power. Health alliances are increasingly drawing on the discoveries from the Human Genome Project and using these to develop treatments for infectious diseases and genetic disorders.

Capacity Building in Science and Technology

The capacity to understand, interpret, and use new life sciences is essential in all countries, for individuals, communities, and institutions. It is vital in a world of 6 billion people, two-thirds of whom live on less than US$2 per day. Political support is essential for science to thrive, and to mobilize financial and policy support.

There is urgency in promoting science and technology worldwide. Science and technology capacity is essential for social and economic development. Several UN agencies, academies of science, and others are committed to enhancing the capacity of developing countries in science and technology. Increased research capacity will enable all countries to access and safely use new technologies, including biotechnology. Capacity building in developing countries is critical, including establishing centers of excellence that meet international standards, and are able to be directed at solving the problems of the resource poor. We need to “think globally, and act locally.”

The next steps will require strong leadership from politicians, business leaders, scientific leaders, and leaders of civil society. We need “humanistic science leaders”

capable of mobilizing science and technology to promote economic and social equity, people who might be called the “new scholars of Alexandria.”

Centers of excellence in science and technology

It is important to foster centers of excellence to concentrate financial and human resources, preferably using a regional approach to their creation and reach. For example, in Africa the New Partnership for Africa’s Development (NEPAD) aims to stimulate the creation of centers of excellence in several areas of science and technology, including the biosciences (see www.biosciencesafrica.org).

The Inter-Academy Council stated in 2004 that “capacity building in science and technology is common sense, but maybe too sensible for the development community to pay attention.” It also points out that no country is too poor for science, and that there is a basic need for science capacity in the South, including applied science. Political vision is important, and reliable data are needed to set baselines and to determine priority programs. Scientists need to be involved in curriculum development to foster interest among children in science. Investing in science teachers should be a priority.

The scientific community must address the questions of meeting infrastructure, information technology, and other needs for developing countries. It should also support excellence in science through competitive grants, merit, and results. It is vital to support centers of excellence, and not to try to do everything everywhere. There should be adequate reward for excellence and results.

The “brain drain” is both a threat and an opportunity. There can be a "brain gain" through mobilizing the diaspora as partners. This would enable scientists to function effectively in their own countries. It would be possible to foster “south-south” collaboration from scientifically capable countries to others, and to support excellence in science.

Next Steps

Concerted actions are required to address the following issues:

- Priority for science and technology at national, regional, and global level.
- Focus on and support for excellence in science and technology, including fostering “centers of excellence.”
- Promote capacity building in science and technology in developing countries.
- Ensure wise use of resources for science and technology.
- Seek to profit and gain from the diaspora, encouraging scientists to contribute to their communities through creative partnerships.

We must seek to foster optimism and commitment for science and society in the future. Future leaders are the key, in science, in society, and in politics. We recognize that there are risks and benefits in science, that may be termed *"Promethean Science" (Serageldin and Persley, 2000). To quote Albert Camus: "We live in a world where children suffer. If I do not help to reduce the number of suffering children, who else in the world will do this?"*

Concluding Thoughts

Steven Jay Gould said it well, in his book the "Rock of Ages", when he referred to non-overlapping magisteria. In it he said that magisteria were "certain rules of which domains of knowledge authority obtain." We find that much of our lives is governed by different magisteria. Science is certainly one and it has its rules and its methodology.

But religion and philosophy are a different domain. If you ask, what is? Science will answer. If you ask, what should I do? That is not a scientific question.

Arts and beauty are a third magisterium. Certainly you cannot judge them either by the questions of morality and religion or by the domain of science alone.

But having recognized that other domains exist, science as we know it, as we practice it today, is an essential part of driving forward the global reality within which we all live. The word "scientist" is very new. It entered the English language only in 1840. In 1900, the Head of the Patent Office in the U.S.A. suggested that the office be closed because it was clear that all possible inventions had already been recorded. Fifty years later, Thomas Watson famously predicted that the global market of computers would never exceed half a dozen or so. So we have not been very good at predicting the future, but perhaps we can get inspiration from looking at the past.

Generally we consider that science has had alternating periods of superior certainty and then anxious uncertainty as things become unraveled. Dunn eloquently complained in 1611 how the new "Copernican notions were creeping into everyone's mind and what is worse they may even well be true!" That was the ultimate! "So the new philosophy calls all in doubt. The element of fire is quite put out. The sun is lost and the Earth and no man's wit can well-direct him where to look for it. And freely men confess that is the world spent when the planets and the [fermemon] they seek so many new and then see that this is crumbled out against these atomies. And in these constellations then arise new stars and old do vanish from our eyes."

To these anxieties, Newton would bring the ordered universe, and the apparent finality of the (principia) was impressive. It led some to believe that you could, if you knew the position of all the molecules at one point, predict where they would be forever into the future.

It was not to be, and it was not to last, and fissures would arise in that elegant structure. And then again, from 1905 to 1919, Einstein gave a glimpse of hope for a new unified theory. But others would cast doubts.

Science advances through bold conjectures and patient empirical analysis. And today it is appropriate that we should celebrate two such brilliant examples.

In 1944, Erwin Schroedinger, a Nobel winning physicist, crossed over into biology and gave outstanding lectures entitled "What is Life?" These were later published under the same title, in which he speculated about life and predicted that the molecule that transmits information necessary for the perpetuation of life, would have a long structure. And that "the aperiodic crystals would play a key role in the creation of order from order." His own words–the fundamental mechanism for heredity and cell replication. This was a bold and shrewd conjecture that was to be vindicated by the epoch-making discovery of the double helix by Watson and Crick in 1953.

Also in 1944, experiments by Oswald Avery, Collin McLoid and Maclin McCarthy showed that a certain nucleic acid, DNA, was the chemical basis for specific and apparently heritable transformations in organisms. This contradicted the then contemporary wisdom suggesting that genes were proteins, even as they were discrete units of heredity, which also control metabolic function. It was an empirical, experimental scientific achievement which regretfully has not been recognized by a Nobel prize to this day.

We salute the spirit of scientists, past and present, who through their dedication and vision are making possible the dawn of a new biology, and a new world, and a new scientific age in the 21st century.

The Getting of Wisdom

To use the words of Daniel Brucestein, the eminent former Librarian of Congress, "Data is running ahead of meaning for most of us." Now data when ordered becomes information, which when interpreted becomes knowledge and which when combined with reflection and experience hopefully yields wisdom. Wisdom will help us deal with the kinds of dilemmas highlighted in our discussions: to select the wisest course of action, to bring the greatest good to the greatest number, without reducing the benefits of any.

We are overwhelmed by a veritable tidal wave of data and information, with precious little knowledge and scarcely any wisdom in an arena where in these dangerous times. Nobelist Walcot said, "where any group can scream injury and litigate against the dead, sue history, demand compensation." It is indeed a dangerous time. People struggle and scream. But it is not he who screams loudest that is necessarily right. The great menace to progress is not just ignorance, but the illusion of knowledge.

Science can contribute much. For if anything has categorized the scientific enterprise, it is the method by which it takes out the spurious from the real; the method by which it improves the accuracy of its analysis. Why are scientists not present enough in this arena? Perhaps it is the nature of their enterprise and for which they have been trained. Perhaps the modern quests for discovery and understanding

yields ever more questions as we provide one answer after another. Our achievements indeed should be measured not in the finality of the answers, but in the fertility of the questions that are raised by our enterprise and our quest. So, let us enjoy the quest together. Let us not seek an ending to it.

We believe that the scientific method and the valleys of science are central to the modernization and development of societies throughout the world. And the promotion of science per se is an integral part of the modernization process. Without it, the social transformation that is implicit in modernization will not take place.

We hasten to add that modernization is not synonymous with copying any particular society. Although there is a central core of universal values that truly any modern society must possess. And these are very much the values that science promotes. Rationality, creativity, the search for truth, adherence to codes of behavior, and a certain constructive subversiveness.

Values are not rules, but they are in Bronowski's beautiful phrase: "those deeper illuminations in whose light justice and injustice, good and evil, means and ends are seen in fearful sharpness of outline." It is a critical thought, in the context of the intolerant debate, that permeates so much of the public discourse in many countries today, where people are judged by the color of their skin, or the God they choose to worship, or the ethnic group they were born into, or their gender. All would agree that the essence of development is a deep humanism, itself defined by a set of profound values that require the scientific outlook and values of science.

The great tradition of Moslem and Arab science did so much for humanity for a thousand years, as the bearers of the torch of knowledge and rationality, as promoters of knowledge like no other – people such as El Khawarezmi, El Razi, Ibn El Nafis, Ibn Sina, Ibn Rushd. These are stellar lights in the history of science and in the history of knowledge. They are our forbearers and we should be their proud disciples. We need to recapture that great tradition. It is our tradition, our history, and our legacy.

We all know that effective pursuit of science, requires the protection of independence. Without the independence of inquiry, there can be no true scientific research. The safeguards that independence requires are also obvious: free inquiry, free thought, free speech, tolerance, and the willingness to arbitrate disputes on the basis of evidence.

These are not just scientific values. These are societal values worth defending, not just to promote the pursuit of science, but to have a better and more humane society. A society that is capable of adapting to change and embracing the new. A tolerant society. Science in its broad context, if not in its details, is accessible to all thinking people because it applies universal tools of the intellect to its distinctive material.

We now extend an invitation to those who function mostly in other magisteria: religion, philosophy, or art, who bring a different sensibility to what is at hand. Let us not have a polarized dichotomy. Indeed dichotomies must interpenetrate and not struggle to the death of one side, because each of their opposite poles captures one

property of an intelligible world. As Goethe said: “the more vitally these two functions of the mind are related, like inhaling and exhaling, the better will be the outlook for the sciences and their friends.”

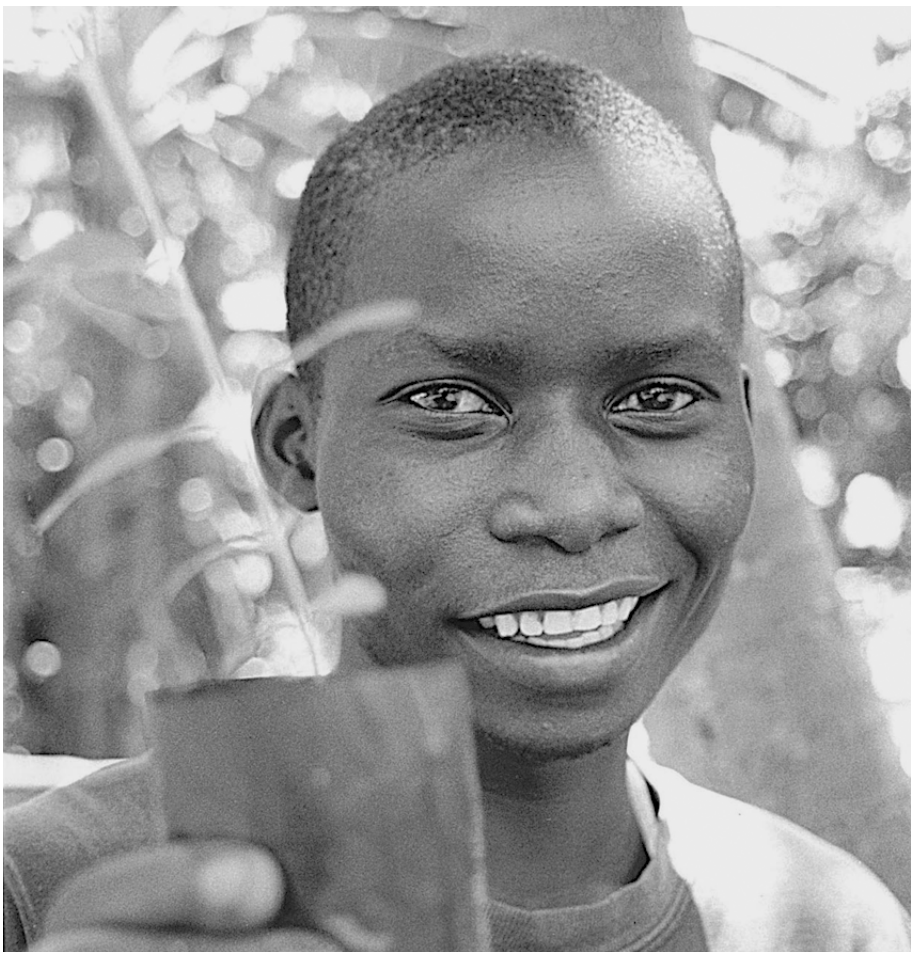
References

Inter-Academy Council. 2004. Inventing a better future: A strategy for building worldwide capacities in science and technology. Full report at www.interacademycouncil.net

Serageldin, I., and G.J. Persley. 2000. Promethean Science: Agricultural Biotechnology, the Environment, and the Poor. Consultative Group on International Agricultural Research, Washington, D.C. 41 p.

Section 3

Agricultural Biotechnology



Chapter 7

Evergreen Revolution: Shifting to an Era of Precision Farming in Rice-Based Systems

M.S. Swaminathan

Introduction

Rice researchers and farmers must move quickly to an era of precision farming, which helps to reduce the cost of production and improve productivity on an ecologically sustainable basis. They should launch a movement to achieve an evergreen revolution in rice farming systems based on ecologically sustainable and location-specific precision farming technologies. Precision farming methods, which can help to enhance income and yield, need to be standardized, demonstrated, and popularized, if a reduction in the cost of production is to be achieved without reduction in yield. A responsive, field-specific management approach will require farmers to monitor crop growth stage, nitrogen status, and pest pressure to precisely identify when N top-dressing, insecticide, or fungicide applications are required. Farmers need to monitor crop growth, and N status, and have access to predictions of growth stage, crop stage, and yield potential from crop simulation models that use real-time weather data and weather projections. This information is crucial for estimating the N fertilizer requirement and the proper timing of N top-dressing and prophylactic treatment against endemic diseases when weather conditions are conducive to disease progression. The revolution in information technology should make it possible for smallholder rice farmers in Asia to access needed information. Without access to such information, it will not be possible to sustain the rate of yield gain needed to meet the demand for rice. A precise match of genotype to environment is needed, while utilizing field-specific tactics to ensure that input requirements are met without deficiency or excess in time and space.

Small Farm Management

Institutional structures, which will confer upon farm families with smallholdings the advantages of scale at the production and postharvest phases of agriculture, are urgently needed. For example, thanks to the cooperative method of organizing milk processing and marketing, India now occupies the first position in the world in milk production. Strategic partnerships with the private sector will help farmers' organizations to have access to assured and profitable marketing opportunities.

There are great opportunities for achieving higher yields per unit of land, water, and time, provided rice farmers are encouraged to shift to precision farming methods. The five vital management areas of research, development, and extension, which need attention from the point of view of achieving environmentally sustainable advances in rice productivity, are:

- Soil health and fertility.
- Water.
- Integrated plant health.
- Energy.
- Postharvest.

Soil health and fertility management

Several studies have shown that the recovery of applied urea in lowland rice can be as low as 20% during the main growing season. In addition, about one-third of applied N is immobilized in the soil. Throughout South Asia, about one-third to one-half of fertilizer N applied to rice crops is lost by leaching, ammonia volatilization, denitrification, and surface runoff. In the USA, global positioning satellites (GPS) are being used to measure soil health properties, such as soil salinity. Use of chlorophyll meters in the management of nitrogen is becoming more widespread. The Silsoe Research Institute in the UK has developed "plant-scale husbandry." This technology involves the use of a high-tech tractor to operate nozzles, which can release precise doses of herbicides, pesticides and fertilizers to plants. Silsoe researchers feel that this method could help reduce the use of chemicals by 90%. Nutrient use efficiency in India could be achieved with the following methods:

- Significant amounts of N could be saved by using a leaf color chart.
- One time application of slow-releasing N fertilizer was better than four applications of urea.
- Combined use of inorganic fertilizer and organic manures such as FYM and compost (up to 25%) was better than sole mineral fertilizers.
- Pre-Kharif (July to October planting season) legume gave 500 kg grain and supplied significant quantities of N to Kharif rice.

- Crop residue incorporation under rice-rice cropping system improved yield and soil properties.

Pulses and oilseeds in rice farming systems

A minimum of 20 kg of nitrogen will be needed to enable the rice plant to produce 1 tonne of rice. At this rate, it will be environmentally disastrous, particularly with regard to groundwater quality, if farmers supply all the needed nutrients for high yields through mineral fertilizers. Pulses and oilseeds are very important for their contribution to human and animal nutrition, as components of indigenous cropping systems, and as restorers of soil fertility. They should be promoted in rice-based production systems of South and Southeast Asia, and interventions introduced that would lead to increased rice and legume production. Inclusion of legumes in the system helps to conserve the natural resource base, particularly soil fertility and groundwater. They can play a significant role in enhancing the factor productivity of a production system. Substantial increases (Greenland, 1997) in the production of rice and pulses can be achieved by promoting high-yielding and short-duration varieties of legumes, and fine tuning management practices. There is a need to explore the feasibility of endowing the rice plant with endosymbiotic nitrogen fixation capacity, because it has significant impact on the global economy and helps improve the environment.

Rice Scientists should foster an "evergreen" revolution in rice through partnerships for the development and dissemination of precision farming technologies. The major goals that were proposed for the FAO-sponsored International Network for an Evergreen Revolution in Rice are:

- Initiate an integrated gene management program.
- Improve productivity per unit of input, particularly of nutrients and water, thereby reducing the cost of production.
- Substitute to the extent possible knowledge and farm produced inputs for capital and market-purchased chemicals.
- Enhance the ecological and social sustainability of high-yield technologies.
- Increase farmers' income and opportunities for skilled employment.
- Establish an information grid and "information villages" for empowering women and men engaged in rice farming, with new knowledge and skills, thereby conferring on rice farmers the strengths of a knowledge society.

Water management

Due to scarcity and competition for water, more research is needed that ties together management of scarce water resources, agronomic practices, and development and

selection of suitable rice varieties. New technology and management practices are needed to increase rice productivity in many of the water-stressed areas bypassed by the green revolution. Water management practices for rainfed and drought-prone areas include a combination of breeding for drought tolerance, and managing limited water supplies to ensure that adequate water is available at critical stages of growth, such as flowering and grain filling. Through better management practices at the farm level, there appears to be ample scope for increasing the productivity of water. There may be a need for systems that produce rice in aerated soil that is saturated with water only when heavy rainfall causes ponding, or after intermittent flood irrigation. Flush irrigation to saturate soil and then allowing soil moisture depletion until a subsequent irrigation would allow even further increase in water-use efficiency. We have no option but to produce more food, feed grain, fiber, fuelwood, and other agricultural commodities per unit of arable land and irrigation water. Arable land and irrigation water are shrinking resources. Therefore, we should move quickly to initiate integrated efforts to develop and master technologies, which can help to usher in an evergreen revolution, or sustainable advances in productivity.

Integrated plant health management

Five diseases (blast, bacterial blight, sheath blight, tungro, and grassy stunt) and four insects (brown planthopper, green leafhopper, stem borer, and gall midge) are of major importance for rice production in tropical and subtropical Asia. Most of the modern varieties contain strong resistance to one or more of these major disease and insect pests. Three genes were successfully transferred for resistance to bacterial blight to new plant type lines via molecular marker-assisted backcross breeding.

Development of varieties with durable resistance to bacterial blight caused by *Xanthomonas oryzae* pv. *oryzae* and for blast caused by *Pyricularia oryzae* was possible as resistance genes have been tagged with molecular markers. Several examples of transgenic rice plants with agronomically important genes are available. In several cases, durable resistance to blast is believed to be associated with quantitative or polygenic inheritance. Under these conditions, there is little or no gain in fitness for a pathogen variant to overcome only a fraction of the polygenes. Breeders should aim at incorporating quantitative or polygenic resistance into rice varieties. Rice plants transformed with *Bacillus thuringiensis* (Bt) were highly toxic to striped stemborer and yellow stemborer. Sources of resistance to some diseases have been identified within cultivated rice germplasm. However, sources of resistance to sheath blight are not available, and there are only a few sources for resistance to tungro disease. A coat protein gene for rice stripe virus was introduced into two japonica varieties, exhibiting a significant level of resistance to virus infection that was inherited by the progenies.

Modern biotechnological tools are available to overcome some of the constraints of conventional tools. Several useful elite lines and improved cultivars were developed using different biotechnological tools.

Energy management

Since fossil fuels are not unlimited, alternate sources of energy must be explored. Renewable sources of energy such as solar, wind or organically produced biogases must be promoted. Increasing hydroelectric power from large dams greatly influences the environment and affects biodiversity. Efficient and environmentally friendly means of providing energy need to be explored, such as blending methanol from sugarcane.

Postharvest management

The scope for reducing postharvest losses remains unclear, which are as high as 20% on a global scale, ranging from 9% in the USA to 40-50% in some developing countries. There is an urgent need to reduce postharvest losses.

Research Strategies and Priorities

Strategies should include integrated gene management (IGM), integrated efforts in feeding and breeding rice for higher productivity, information empowerment, and overcoming hidden hunger caused by micronutrient deficiencies. Rice could also be promoted as a substrate for oral vaccines.

Integrated gene management

The IGM program in rice should be based on the three goals of the Convention on Biological Diversity (CBD): conservation, sustainable use, and equitable sharing of benefits.

Conservation

In this area, rice research organizations should strive to strengthen the continuum in situ, in situ-on farm, and ex situ methods of conservation of agrobiodiversity.

National rice research systems should have well-defined plans and programs in the areas of ex situ preservation in gene banks and in situ on-farm conservation by farmers, through participatory breeding and market linkages. The 100,000-plus strains available today in rice are the result of the conservation ethics of farm and tribal families. Most of them are from Asian countries. India is the largest contributor to this collection followed by Laos. I am a strong proponent of recognizing and rewarding farmers for their invaluable contributions to conservation of farm varieties that are essential for rice improvement (Swaminathan, 2003a, b).

Sustainable use

The vast ex situ collections in the genebanks are utilized in a limited way. Value addition through participatory breeding and varietal selection, characterization, and evaluation could promote their utilization. Farmers' knowledge about the samples collected and conserved would also promote their use. Lao farmers assign names to varieties that describe the most important traits–maturity, types of endosperm (glutinous or nonglutinous), adaptation (wetlands, drylands, and garden lands), and others. Some of the names like forgot husband (very tasty), dog stares at it (poor eating quality), and aroma (aromatic flowers) help to identify appropriate accessions from the vast collections. We should promote a system of integrated standard and molecular breeding and distribution of novel genetic combinations to rice breeders, to develop location-specific varieties designed to promote ecologically desirable agricultural practices. Molecular linkage maps have made it possible to identify and study the effects of the individual loci that control a quantitatively inherited trait. Such quantitative trait loci can help to improve characters controlled polygenically.

We should prevent nutritious crops becoming "lost crops," by having more participatory breeding and by creating an economic stake in their conservation, and by including them in crop rotations in rice-based cropping systems. A distinctive contribution should include enlarging the composition of the food basket by including minor and underutilized crops, which are often rich in micronutrients, in rice farming systems. Such crops are often ecologically well adapted and can be of considerable significance to household nutrition security.

Equity in sharing benefits

- Strengthen steps to prevent misappropriation of germplasm held in trust under agreement with FAO.
- Assist FAO in finalizing the revised international undertaking on genetic resources and assist in getting it included as a protocol under CBD.
- Work with FAO in promoting a multilateral system of exchange of genetic resources in crops of importance to food and nutrition security.

- Intensify efforts in gathering information relevant to the equitable sharing of benefits with the conservers of genetic resources and holders of traditional knowledge, so that the concept of Farmers' Rights becomes a reality.
- Promote the integration of the principles of equity and ethics in the use of genetic resources and information at the international level.

Integrated efforts in feeding and breeding rice for high productivity

Recent estimates of rice demand indicate that a compound annual growth rate of 1.25% is needed to meet expected rice consumption by 2020. The projected increase in rice demand must be met entirely by greater output per unit area on existing rice land. Meeting projected rice demand will depend on sustaining an adequate rate of gain in average rice yields on existing irrigated land. With increasing population, global rice production needs to be increased from the 1995 level of 460 million tonnes to 980 million tonnes by 2020.

At current levels of nitrogen use efficiency, this will involve a doubling of the 10 million tonnes of nitrogenous fertilizers that are currently being used each year for rice production worldwide. There is a heavy loss of applied nitrogenous fertilizers because rice cannot make use of the N supplied. Improved water management and agronomic practices will help to reduce losses. In addition, three basic approaches have been proposed to solve this problem. One is to regulate the timing of N application based on the needs of the plants, thus partly increasing the efficiency of the use of applied nitrogen. The second is the introduction of integrated nutrient supply systems involving green manures, biofertilizers, compost, and other forms of organic manures, along with the minimum essential quantities of mineral fertilizers.

Increase the ability of rice to fix its own nitrogen

New frontiers of science offer exciting opportunities to investigate the possibilities of incorporating N fixation capacity in rice. It is now well over 100 years since the existence of microorganisms capable of biological fixation of atmospheric nitrogen was experimentally proved, and nitrogen-fixing capacity of legume-rhizobia symbiosis was established. Since then, this symbiotic system has been well understood and exploited as an effective means of raising the nitrogen status of soil and for providing nitrogen for crops and pastures. Optimism that nonleguminous crops could similarly benefit was fueled in the 1970s and 1980s with the discovery of several nitrogen-fixing organisms forming specific association with nonlegumes. Several approaches, including the use of molecular mapping and breeding methods, have raised fresh hopes that success in this field could be achieved in the near future. Several discoveries in this area suggest that symbiotic nitrogen fixation can be

extended to nonlegumes. The transfer of *nif* genes, together with others necessary for functional nitrogen fixation into chloroplasts, was believed to be the best strategy to achieve this. However, the complexity of gene regulation remains a major hindrance in achieving a functional nitrogen fixing transgenic system. Significant advances have been made in recent years in the induction of nodule-like structures in rice roots by rhizobia, and establishing an endophytic system in rice. These results, along with recent technical advances involving the induction of nodular structures on the roots of cereal crops such as wheat and rice, offer the prospect that dependable symbiosis with free-living diazotrophs, such as azospirillum, or with rhizobia can eventually be achieved. Ultimately, we should package all such opportunities into an integrated soil health care and fertility system. This is a vital component of an evergreen revolution. Yuan (1998) has described the opportunities for the spread of hybrid rice. Research on feeding for high yield should proceed concurrently with breeding for high yield. Otherwise, large doses of mineral fertilizers will have to be applied, with harmful long-term ecological consequences, to realize the yield potential of "super-rices."

Knowledge and information empowerment

A global knowledge system for rice would offer tremendous opportunities to improve the efficiency and effectiveness of networks. Information empowerment holds the key to successful ecological rice farming. The following steps will be useful:

- Develop an interactive, two-way learning system.
- Train value-adders who can convert generic information into location-specific data.
- Develop a system that can reach farm and rural women, in particular, in terms of information and skill empowerment.
- Harness modern information technology to spread awareness and understanding of dying wisdom and traditional knowledge systems, particularly water harvesting and coping with unfavorable weather conditions.
- Establish "information villages" in principal rice-growing areas to take the benefits of modern information technology to rice-farming families, in areas of new material, management practices, and marketing opportunities. This will be an essential prerequisite for initiating an era of precision farming in rice.

Overcoming hidden hunger caused by micronutrient deficiencies

The challenge of micronutrient deficiencies in the diet is growing. Iodine, vitamin A, and iron deficiencies are serious in many parts of the developing world. Globally, iron deficiency affects over one billion children and adults. Recent analyses from the

United States Institute of Medicine highlight the effect of severe anemia resulting in one in five maternal deaths. Maternal anemia is pandemic and is associated with high morbidity and mortality rates; anemia during infancy, compounded by maternal undernutrition, leads to poor brain development. Iron deficiency is also a major cause of permanent brain damage and death in children, and limits the work capacity of adults. There is not enough appreciation of the serious adverse implications to future generations arising from the high incidence of low birth weight (LBW) among newborn babies. LBW is a major contributor to stunting and affects brain development in the child.

The new millennium will be a knowledge century, with agriculture and industry becoming more knowledge intensive. Denial of opportunities for the full expression of the innate genetic potential for mental development, even at birth, is the cruelest form of inequity that can prevail in any society. We must take steps to eliminate as soon as possible such inequity at birth, leading to a denial of opportunities to nearly one out of every three children born in South Asia.

Wherever rice is the staple, a multipronged strategy for the elimination of hidden hunger should be developed by rice scientists. IRRI has undertaken research on enriching rice genetically with iron and other micronutrients. Fortification, promotion of balanced diets, new semiprocessed foods involving an appropriate blend of rice and micronutrient rich millets, as well as genetic improvement, could all form part of an integrated strategy to combat the following major nutritional problems in predominantly rice-eating families:

- Protein-energy malnutrition.
- Nutritional anemia (iron deficiency).
- Vitamin A deficiency.
- Iodine deficiency.
- Dietary deficiencies of thiamin, riboflavin, fat, calcium, vitamin C, and zinc.

I suggested that the International Rice Commission could include nutrition security aspects as an integral part of the International Network (Swaminathan 2003b). We must fight the serious threat to the intellectual capital of developing countries caused by low birth weight children and hidden hunger. Some of the research areas worthy of attention in this context are described below.

Challenges Ahead

While we can and should rejoice about the achievements of farmers, scientists, extension workers, and policymakers, there is no room for complacency. We still face several new problems, of which the following are most important:

- Increasing population leads to increased demand for food and reduced per capita availability of arable land and irrigation water.

- Improving purchasing power and increasing urbanization lead to higher per capita food grain requirements due to an increased consumption of animal products.
- Marine fish production is tending to become stagnant and coastal aquaculture has resulted in ecological and social problems.
- Damage to the ecological foundations of agriculture, such as land, water, forests, biodiversity, and the atmosphere is increasing; and there are distinct possibilities for adverse changes in climate and sea level.
- Dramatic new technological developments are taking place, particularly in biotechnology, but environmental, food safety, and social implications are not yet fully understood.
- Gross capital formation in agriculture is now tending to decline in public and private sectors. The rate of growth in rural nonfarm employment has been poor.

Since land and water will be shrinking resources for agriculture, there is no option in the future but to produce more food and other agricultural commodities from less per capita arable land and irrigation water. In other words, the need for more food has to be met through higher yields per unit of land, water, energy, and time. It would therefore be useful to examine how science can be mobilized to raise further the ceiling to biological productivity without associated ecological harm. We refer to the emerging scientific progress on the farms as an "evergreen revolution," to emphasize that the productivity advance is sustainable over time, since it is rooted in the principles of ecology, economics, social and gender equity, and employment generation.

The green revolution based on traditional breeding practices has so far helped to keep the rate of growth in food production above the population growth rate. The green revolution was, however, the result of public good research, supported by public funds. The technologies of the emerging gene revolution based on molecular genetics, by contrast, are spearheaded by proprietary science, and can come under monopolistic control. How can we take the fruits of the gene revolution to the unreached?

Major challenges that will confront crop scientists during the next 20 years or so include:

Ecology

Ecological sustainability of high productivity will be an important determinant in relation to the choice of technologies. For example, if hybrid wheat can enable us to produce 8 to 10 t/ha, over 300 kg of nitrogen will be needed by the crop. It is obvious that if the nutrient needs of hybrid or other high-yielding wheat or rice varieties are to be met entirely through mineral fertilizers, there will be serious environmental problems, including nitrate pollution of groundwater. Hence, success in achieving high productivity on a sustained basis will depend upon our ability to develop new

methods of feeding the plant. Research on breeding and feeding the plants should be carried out concurrently by a team of breeders, physiologists, agronomists, and soil scientists.

Equity

The Convention on Biological Diversity stipulates that plant exploration, collection, and introduction should be based on the principles of prior informed consent and equity in benefit sharing. FAO has also developed an International Treaty on Genetic Resources in Food and Agriculture. Therefore exchange of crop genetic resources in the future will be possible only based on Material and Knowledge Transfer Agreements.

Concerns relating to genetically modified organisms

Molecular genetics and recombinant DNA technology have opened new opportunities in agriculture, medicine, industry, and environment protection. The ability to move genes across sexual barriers has led to heightened interest in the conservation and sustainable and equitable use of biodiversity, since biodiversity is the feedstock for plant, animal, and microbial breeding enterprises.

Considerable advances have been made during the last 25 years in taking advantage of the new genetics in the areas of medical research, production of vaccines, sero-diagnostics and pharmaceuticals for human and farm animal health care. The production of novel bioremediation agents, for example the development of a new *Pseudomonas* strain for clearing oil spills, is also receiving priority attention because There has also been substantial progress in agriculture, particularly in the area of crop improvement using molecular marker-assisted breeding, functional genomics, and recombinant DNA technology. A wide range of crop varieties containing novel genetic combinations are now being cultivated in the USA, Canada, China, Argentina, and elsewhere. A strain of cotton containing the *Bacillus thuringiensis* gene (Bt Cotton), which has resistance to bollworms, is now under cultivation. Besides cotton, the largest areas in the world under genetically modified varieties are in corn, soybean, and canola (James, 2004).

There is little doubt that the genetics has opened opportunities for enhancing the productivity, profitability, sustainability, and stability of major cropping systems. It has also created scope for developing crop varieties tolerant/resistant to biotic and abiotic stresses, through an appropriate blend of standard and molecular breeding techniques. It has led to the possibility of undertaking anticipatory breeding to meet potential changes in temperature, precipitation, and sea level because of global warming. There are new opportunities for fostering pre-breeding and farmer-participatory breeding methods to continue the merits of genetic efficiency with genetic diversity.

Although the benefits are clear, there are also many risks when we enter the territory of the unknown and unexplored. Such risks relate to potential harm to the environment and to human and animal health. There are also equity and ownership issues in relation to biotechnological processes and products. The following issues are the major areas of concern to the public and policymakers.

- What is inherently wrong with the technology? Is the science itself safe, for example the use of selectable marker genes conferring antibiotic or herbicide resistance?
- Who controls the technology? Will it be largely in the private sector? If the technology is largely in the hands of the private sector, the overriding motive behind the choice of research problems will be private profit and not necessarily public good. If this happens, "orphans will remain orphans" with reference to choice of research priorities. Crops that are being cultivated in rainfed, marginal and fragile environments may continue to remain neglected.
- Who will have access to the products of biotechnology? If the products arising from recombinant DNA technology are all covered by intellectual property rights, then the technology will result in social exclusion and will lead to a further enlargement of the rich-poor divide in villages.
- What are the major biosafety issues? There are serious concerns about the short- and long-term impact of genetically modified organisms (GMOs) on the environment, biodiversity, and human and animal health.

Thus, there is need for transparent and truthful risk-benefit analysis in relation to GMOs, on a case-by-case basis. In the coming years, Indian farmers will have to produce more food and other agricultural commodities to meet home needs, and to take advantage of export opportunities, under conditions of diminishing arable land and irrigation water, and expanding abiotic and biotic stresses. The enlargement of the gene pool with which breeders work will be necessary to meet these challenges. Recombinant DNA technology provides breeders with a powerful tool to enlarge the genetic base of crop varieties, and to pyramid genes for a wide range of economically important traits. The safe and responsible use of biotechnology will enlarge our capacity to meet the challenges ahead, including those caused by climate change. At the international level, the Cartagena Protocol on Biosafety provides a framework for risk assessment and risk aversion. At the national level, there is need for a regulatory mechanism that inspires public, political, and professional confidence.

Expansion of proprietary science

The world is witnessing an expansion of proprietary science governed by intellectual property rights. The green revolution was the outcome of public-good research. Unfortunately, public-good research supported from public funds, in contrast, is shrinking. What will be the impact of such a situation on international varietal or other trials organized by the international agricultural research centers of the Consultative Group on International Agricultural Research? Is the golden age of cooperative research ending? How can we find a balance between public good and private profit? Will the fruits of the gene revolution triggered by molecular breeding be available to resource-poor farmers?

Climate change and safeguarding genetic diversity

Will molecular breeding based on intellectual property rights lead to a high degree of genetic homogeneity in farmers' fields? We know that genetic homogeneity will enhance genetic vulnerability to biotic and abiotic stresses. Hence, we should foster an integrated program of pre-breeding and participatory breeding. Pre-breeding will help to generate novel genetic combinations, whereas participatory breeding with farm families will help to combine genetic efficiency with genetic diversity. Numerous location-specific varieties can be developed in this manner. This will be the most effective way of meeting challenges arising from potential changes in temperature, precipitation, and sea level as a result of global warming arising from the growing imbalance between carbon emissions and absorption.

Conclusion

Scientists and policymakers must continue to work together and share ideas and material, if the challenge of sustainable food security is to be met. The Biovision Alexandria 2004 conference demonstrates to the world the power of partnership. We hope this marks the beginning of a new era of international partnership among scientists dedicated to the cause of harnessing the best in science, to contribute to the achievement of the UN Millennium Development Goals in the area of hunger and poverty.

References

Greenland, D.J. 1997. The Sustainability of Rice Farming. International Rice Research Institute, Los Banos, Philippines. 273 p.

James, C. 2004. Global status of commercialized Biotech/GM crops: 2004. International Service for the Acquisition of Agri-Biotech Applications. ISAAA Brief No. 32. ISAAA, Los Banos, Philippines. 43 p.

Swaminathan, M.S. 2003a. Biodiversity: an effective safety net against environmental pollution. Environmental Pollution, 126 (3): 287-291.

Swaminathan, M.S. 2003b. Nutrition security and natural resources scarcity in Asia. Quality Journal of International Agriculture, 42 (3): 241-260.

Chapter 8

Harnessing New Science for Sustainable Agriculture in Dry Areas

Adel El-Beltagy

Introduction

There is a survival paradox facing the world today: feeding the ever-increasing population, while preserving the health of the earth, amidst expanding natural resource constraints. Predictions are that global food requirements will double by 2020.

Close to 5 billion or 80% of the world's population live in developing countries, and an estimated 1 billion inhabit the dry areas. Of the 690 million people living in the dry areas of the West Asia and North Africa (WANA) region, some 76% have a mean per capita income of less than US$2 a day, and about 42% live on US$1 a day.

Doubling food production by 2020 needs expansion of agricultural land, but most of the world's prime land is already under cultivation. The world's land area occupies about 13 billion hectares, 3.36 billion of which is rangeland, and only 1.44 billion is arable. Of this small arable area at our disposal to feed the world, 240 million hectares are irrigated. According to UN estimates, more than 50% of the world's irrigated land faces some form of degradation problems.

This scenario is worsened by desertification. The world loses more than 6 million hectares of land yearly to desertification. Over 100 countries and 20% of the world's population are affected. These deserts differ from the "natural" ones in that they are created by people. Their origins can be traced, and they can be controlled, if the causes are recognized early enough. The continued loss of vegetation as a result of land degradation also depletes the world's biodiversity, which holds precious genes for developing new crop varieties for the future. It also reduces the ability of the landscape for carbon sequestration, with the consequent long-term effects of global warming and climate change.

In the dry areas, the key natural resource is, of course, water. Globally, about 97.5% of water is salty. Fresh water in lakes, reservoirs, and rivers amounts to only 0.007% of the total. Irrigation accounts for 67% of water withdrawn from the hydrological cycle, and industry 23%. The world data on water resources indicates

that the WANA region faces the most serious threat of water shortages. The average annual per capita renewable water supply in WANA countries is now less than 1500 m^3 (less than one-fourth of the world average). This level is expected to fall to less than 700 m^3 by 2025. In 1990 only 8 of the 23 WANA countries had per capita water availability of more than 1000 m^3, the threshold for water poverty level. It is projected that at least 19 WANA countries will reach the acute water poverty level by 2050.

Yet another challenge, especially for the dry areas, is drought. It is one of the major abiotic stresses limiting productivity of field crops in rainfed agriculture. Drought is unpredictable and its severity depends on many factors, including the amount and distribution of rainfall during the cropping season, evaporative demand of the atmosphere, and the capacity of the soil to conserve moisture. Selection and breeding for drought tolerance becomes even more complex due to the interactions of drought with other abiotic stresses such as heat and cold, and even biotic stresses that reduce the ability of plants to withstand drought.

Given these challenges, the world community faces a tough choice; we either invest in the available tools of science to enhance food security, or perish. Knowing that the land area cannot be expanded and the ongoing global climate change will demand new crop varieties that can withstand the abiotic and biotic stresses of the future, new tools of science, particularly those in biotechnology and information technology, offer great promise in safeguarding the global future food security.

ICARDA and the CGIAR

The International Center for Agricultural Research in the Dry Areas (ICARDA) argues optimistically that human ingenuity can find ways to deal with the scarcity of natural resources. ICARDA is one of the 15 international agricultural research centers under the umbrella of the Consultative Group on International Agricultural Research (CGIAR). ICARDA's mission is to improve the welfare of people in the dry areas of the developing world, by increasing the production and nutritional quality of food, while preserving and enhancing natural resources. The Center pursues this challenge through research, training, and dissemination of information in partnership with national agricultural systems and governments.

ICARDA has global and regional mandates. It has a global responsibility for the improvement of three important food crops (barley, lentil, and faba bean) and sustainable management of natural resources in the dry areas, especially enhancing on-farm water-use efficiency. The Center's regional responsibility focuses on the improvement of wheat, chickpea, and forage and pasture crops in Central and West Asia and North Africa (CWANA).

Our strategy is to engage national agricultural research systems in the region and advanced agricultural research centers from all over the world into a research continuum that ensures that tools of modern science are harnessed to meet the challenges of agriculture in the dry areas. There are numerous examples to show that it is working.

Genetic resources characterization

Biodiversity conservation at ICARDA responds to the Leipzig Global Plan of Action for the Conservation and Sustainable Utilization of Plant Genetic Resources of National Agricultural Research Systems (NARS), and to the CGIAR stripe review of plant genetic resources. ICARDA holds the largest gene bank in the Mediterranean region, with about 131,000 accessions that represent approximately 20% of the germplasm in CGIAR centers. Particularly important are the landraces and wild relatives that have evolved under harsh conditions over millennia. About 70% of our collections are now geo-referenced. This collection-site information combined with climatic layers in GIS (global information systems) allows targeted collection and a rapid exploitation of accessions with tolerance to drought and heat to meet the anticipated effects of climate change. ICARDA has been freely sharing these resources with global partners. On average, the Center distributes 35,000 samples yearly. Overall, the shift from collection and *ex situ* conservation of plant germplasm to its characterization, evaluation, and documentation will help to utilize the biodiversity held at ICARDA.

A number of DNA fingerprinting techniques (microsatellites or Simple Sequence Repeat (SSR), Amplified Fragment Length Polymorphism (AFLP) and Single Nucleotide Polymorphism (SNP) markers) are used for fingerprinting plant genetic resources at ICARDA (Sasanuma *et al.,* 2002, 2004; Udupa *et al.,* 1999; Eujayl *et al.,* 2002; Chabane *et al.,* 2004). Expressed-sequence tags (EST) databases provide opportunities for gene discovery, and such databases also provide a novel source of microsatellites (SSRs) that are physically associated with coding regions of the genome (EST-derived SSRs; Eujayl *et al.,* 2002). Genomic SSRs as well as EST-derived SSRs are currently being used to genotype germplasm collections (Udupa *et al.,* 1999).

Intraspecific and interspecific genetic variation was investigated in seven diploid *Aegilops* species using the amplified fragment length polymorphism (AFLP) technique (Sasanuma *et al.,* 2004). Of the seven species, the cross-pollinating *Aegilops speltoides* and *Ae. mutica* showed high levels of intraspecific variation, whereas the remaining five self-pollinating species showed low levels. *Ae.s bicornis*, *Ae. searsii* and *Ae. speltoides* formed one, while *Ae. caudata* and *Ae. umbellulata* formed another cluster in the dendrograms. Relationships among the species inferred were more consistent with the relationships inferred from studies of chromosome pairing in interspecific hybrids, and previous molecular phylogenetic reconstructions based on nuclear DNA, than they were with those based on molecular plasmon analysis. This suggests that the nuclear genome has evolved differently from the cytoplasmic genome in the genus *Aegilops.*

Ecoregional haplotyping

In order to examine how molecular polymorphism in barley landraces, sampled from five different ecogeographical regions of Syria and Jordan, is organized and partitioned, genetic variability at 21 nuclear and 10 chloroplast microsatellite loci was examined (Russell *et al.,* 2003). Chloroplast polymorphism was detected, with most variation being ascribed to differences between the five regions (Fst 0.45) and to within sites within each region (Fst 0.44). Moreover, the distribution of chloroplast polymorphism is structured and not distributed randomly across the barley landraces sampled. From a total of 125 landrace accessions (five lines from each of five sites from each of five regions) genotyped with 21 SSRs a total of 244 alleles were detected, of which 38 were common to the five regions sampled. Most nuclear variation was detected within sites. Significant differentiation between sites (Fst 0.29) was detected with nuclear SSRs, and this partially mirrored polymorphism in the chloroplast genome. Strong statistical associations/interactions were also detected between the chloroplast and nuclear SSRs, together with nonrandom association (linkage disequilibrium) of alleles at both linked and unlinked SSR loci. These results showed that so-called “adapted gene complexes” and the assembly of favorable interacting alleles into synergistic complexes arising from gametic-phase disequilibrium, is highly relevant to the evolution of landraces.

Tilling

We are employing ECOTILLING technology, a variant of the better known TILLING method (Targeting Induced Local Lesions In Genomes; Comai *et al.,* 2004) for high-throughput detection of allelic variations such as SNPs in pathogen or abiotic stress resistance genes. We use ECOTILLING to search for natural allelic variation in segments of resistance genes in selected core collections. ECOTILLING detects allelic variants of genes by amplification of the same part of a gene from up to eight different individuals from naturally occurring plant accessions in the same polymerase chain reaction (PCR) mixture. During the final elongation step of the PCR reaction, the two DNA strands re-anneal and either form homoduplexes if all DNA strands are perfectly complementary, or heteroduplexes if mutations are present in one or the other DNA strand that result in mismatches within the newly formed DNA double strands. These mismatches represent allelic variants of a gene. The amplified gene fragments are then subjected to digestion with the endonuclease CEL I and denaturing PAA gel electrophoresis. Allelic variant of genes of interest can be identified (Comai *et al.,* 2004) with the technique and be sequenced.

Genome mapping

DNA molecular marker techniques allow construction of linkage maps for crops. Together with statistical techniques, these linkage maps can be used to locate and estimate phenotypic effects of quantitative trait loci (QTL) and the genes responsible for the expression of agronomic traits. For a homozygous population derived from a cross with parents contrasting in response to, for example, water, QTL analysis reveals the approximate map location of loci associated with performance under dryland conditions. This is then amenable to marker-assisted selection using DNA markers flanking the identified QTLs.

A genetic linkage map has been developed for recombinant inbred lines (RILs) of the cross 'Arta' x *Hordeum spontaneum* 41-1 (Baum *et al.*, 2003). One-hundred and ninety-four RILs, randomly chosen from a population of 494 RILs, were mapped with 189 markers including one morphological trait (*btr* = brittle rachis locus). The linkage map extended to 890 cM. Agronomic traits such as grain yield, biological yield, days to heading, plant height, and cold tolerance were evaluated at the ICARDA research stations Tel Hadya and Breda in 1996-97 and 1997-98. QTLs for agronomic traits related to drought resistance were localized. For the most important character, "plant height under drought stress," QTLs on 2H, 3H, and 7H were detected. The "plant height" QTLs, especially the one on 3H, showed pleiotropic effects on traits such as days to heading, grain yield and biological yield. QTLs were also identified for other traits associated with adaptation to the Mediterranean environment such as cold tolerance, days to heading, and tiller number. The identification of QTLs for agronomic traits is a first step to analyze and to dissect complex characters such as adaptation to drought tolerance.

A durum-dicoccoides genetic linkage map was constructed using 124 microsatellites, 149 AFLPs, and six seed storage proteins (SSP) in a population of 114 recombinant inbred lines (F8) (Elouafi *et al.*, 2001). The population has been obtained from a cross between a durum cultivar Omrabi5 and Triticum dicoccoides600545 and backcrossed to Omrabi5. The map consists of 14-durum chromosomes plus an unknown group, and shows a good synteny to the previously published wheat maps. Yellow pigment was measured in the population in three different locations during three seasons. Analysis of QTLs was based on simple and simplified composite interval mapping (SIM and sCIM). Three QTLs for yellow pigment were detected on the chromosomal group 7 (7AL and 7BL telomeres) explaining 62% of the total variation. On 7BL, a major microsatellite (Xgwm344) explained by itself 53%, whereas on 7AL, the other two QTLs have contributed 13 and 6%. All determined QTLs showed a strong genetic effect and a weak QTL x E effect. The QTLs effect was consistent across all environments and showed a large effect. Consequently, promising QTLs will be used in the marker assisted breeding program to enhance the selection efficiency for yellow pigment.

Tissue culture techniques: grass pea

Grass pea *(Lathyrus sativus)* is the most drought-tolerant legume that is used as feed and food in many countries such as Ethiopia, Bangladesh, China, India, and Nepal. Consumption of grass pea seeds in large quantities by humans and animals can lead to "lathyrism" or paralysis of the legs, because of the presence of a neurotoxin in the seeds. Recently, existing protocols for explant culture of *L. sativus* have been used at ICARDA (Abd-El-Moneim *et al.,* 2000). Somaclones showed high variation for morphological traits as well as for ß-ODAP. Somaclonal lines were identified that expressed consistent lower levels of the neurotoxin. These are being multiplied in Ethiopia after testing.

Transformation technology

Since the mid 1980s, it has become possible to isolate genes from any class of living organism and introduce them into most of our crop plants (Dale, 2000). This provides a wider choice of genes for crop improvement than is available by conventional plant breeding. In 2003, there were over 50 million hectares of transgenic crops grown across the world (James, 2003), and about 70% of the GM crops were herbicide resistant. Without entering into a controversial GM debate, there are a number of cases where the testing of GM materials seems to be justified (for example, herbicide resistance to control parasitic weeds *Orobranche* ssp., in legumes; fungal and insect resistance in legumes).

Progress in transformation of large-seeded legumes has been extensively reviewed (Somers *et al.,* 2003). Historically, both microprojectile bombardment and *Agrobacterium* have been used for DNA delivery into either embryogenic or organogenic cultures of some species that have been subjects of extensive research. Although transformation systems are available now for chickpea, lentil, and faba bean, their efficiency needs to be improved. Efficient transformation and regeneration systems are available for cereals such as wheat (Pellegrineschi *et al.,* 2002) and barley (Murray *et al.,* 2004).

ICARDA is exploring the possibility of using genetic transformation to achieve improved tolerance to fungal, drought and other abiotic stress resistance. Chickpea transformation is being done in cooperation with the University of Hannover, Germany. Lentil transformation is being done in cooperation with the Centre for Legumes in Mediterranean Agriculture (CLIMA), Australia. Cereal transformation is being carried out jointly with the Agricultural Genetic Engineering Research Institute (AGERI) in Cairo, Egypt.

National and regional biosafety frameworks

ICARDA actively promotes the development and establishment of national and regional biosafety regulations. By early 2004, Egypt and Syria were the only countries in the region that had established biosafety regulations. In several other countries preparations for the development of biosafety regulations are underway. ICARDA is engaged in the development of genetically modified crops to increase biotic and abiotic stress resistance in its mandated crops (barley, lentil, and faba bean). ICARDA's policy is guided by international biosafety practices and the regulations of the Syrian Arab Republic for the development and deployment of genetically modified organisms (GMOs). ICARDA is promoting biosafety regulations together with national, regional and international organizations (Baum, *et al.,* 2001). ICARDA will use as much as possible "plant genes" for its genetic engineering approach. Selectable markers are currently being used, but will soon be replaced with biologically imperceptible markers as soon as alternative appropriate technologies become available. On a case-by-case basis, ICARDA will evaluate potential risks associated with development and deployment of GMOs. For transfer of GMOs to national programs, ICARDA will follow national or regional regulations. ICARDA will not deploy GMOs in any country lacking such regulations. Only well characterized GMOs that have been field tested at ICARDA and that have been inspected by national program scientists will be considered for distribution to NARS.

Functional genomics for drought tolerance

Developments in large-scale, high-throughput technologies and robotics now allow researchers to simultaneously profile vast numbers of different genes or proteins in parallel. Microarrays are at the center of the revolution of biotechnology for functional genomics, allowing researchers to screen tens of thousands of genes simultaneously in multiple tissues under a myriad of experimental conditions. This is significantly different from the classical idea of investigating one (or a few) genes at a time.

Considerable complexity has been demonstrated by the analysis of drought responses by transcript profiling using microarrays. Cold, drought and salinity stress regulated many genes in *Arabidopsis* (Seki *et al.,* 2001). Many genes were affected by drought and salinity (119 up-regulated, 31 down-regulated), and a smaller number by drought and cold. A relatively large number (22 up-regulated, 17 down-regulated) are affected by all stresses (Seki *et al.*, 2001). Similarly, barley data showed up- and down-regulation at a given treatment overlapping only partially with genes regulated by a different stress (Öztürk *et al.*, 2002).

ICARDA is developing drought microarrays (in collaboration with the Institute for Genome Research, TIGR, IPK-Gatersleben, Germany; and AGERI, Egypt) to help characterize the different pathways to stress tolerance, and elucidate their interdependent genetic control. We believe this will enable us to pyramid several unique mechanisms of drought tolerance in our legume and cereal crops for the rainfed regions of CWANA, and will lead to improved crop yield stability and reliability.

CGIAR Generation Challenge Programs

ICARDA is a consortium member participating in the CGIAR-sponsored Generation Challenge Program "Unlocking Genetic Diversity in Crops for the Resource-Poor." This Challenge Program will produce a new, unique *public platform* for accessing and developing new genetic resources using molecular technologies and traditional means. The Challenge Program's development goal is to increase food security and improve livelihoods in developing countries. This will be achieved by unlocking the genetic potential and enhancing the use of public genetic resources in plant breeding programs, through the concerted generation, management, dissemination, and application of comparative biological knowledge. The Generation Challenge Program contributes to this goal by creating an integrated platform for dissecting genetic diversity in plant genetic resources, identifying important genes to reduce the impacts of environmental and biotic stresses on crop productivity, enhancing yield, and improving nutritional quality of crop products. Beyond this, the Generation Challenge Program will identify, manipulate, and validate gene expression resulting in plants with potential value far beyond present-day crops. These plants, through seeds or vegetative propagules, will be transferred to breeding programs. The Generation Challenge Program will generate new, science-based enabling and intermediate technologies. A technology transfer plan will be designed to ensure that the products of research will be delivered to and used by plant breeders and farmers. Further information is available at www.generationcp.org.

References

Abd-El-Moneim, A., B.M. Van Dorrestein Baum *et al.* 2000. Improving the nutritional quality and yield potential of grasspea (Lathyrus sativus L). Food Nutri. Bull. 21:493-496.

Baum, M., A. De Kathen, and J. Ryan. (eds). 2001. Workshop on developing and harmonising biosafety regulations for countries in West Asia and North Africa (WANA), ICARDA, Aleppo, 163 p.

Baum, M., S. Grando, G. Backes *et al.* 2003. QTLs for agronomic traits in the Mediterranean environment identified in recombinant inbred lines of the cross 'Arta' x H. spontaneum 41-1. Theor Appl Genet. 107(7): 1215-25.

Chabane, K., G.A. Ablett, G.M. Cordeiro, J. Valkoun, and R.J. Henry. 2004. EST versus genomic derived microsatellites for genotyping wild and cultivated barley. Genetic Resources and Crop Evolution (in press).

Comai, L., B.J. Till, S.H. Reynolds *et al.* 2004. Large-scale discovery of natural polymorphisms by ecotilling. Plant Journal 37: 778-786.

Dale, P.J. 2000. The GM debate: science or scaremongering? Biologist (London). 47(1): 7-10. Review.

Elouafi, I., M.M. Nachit, and L.M. Martin. 2001. Identification of a microsatellite on chromosome 7B showing a strong linkage with yellow pigment in durum wheat (Triticum turgidum L. var. durum). Hereditas 135: 255-261.

Eujayl, I., M.E. Sorrells, M. Baum *et al.* 2002. Isolation of EST-derived microsatellite markers for genotyping the A and B genomes of wheat. Theor Appl Genet. 104: 399–407.

James, C. 2003. Preview. Global review of commercialized transgenic crops: 2003. ISAAA Briefs 12: Preview, Ithaca, N.Y., 8S.

Murray, F., R. Brettell, P. Matthews *et al.* 2004. Comparison of Agrobacterium-mediated transformation of four barley cultivars using the GFP and GUS reporter genes. Plant Cell Rep. 22(6): 397-402.

Öztürk, Z.N., V. Talamé, M. Deyholos *et al.* 2002. Monitoring Large-Scale Changes in Transcript Abundance in Drought- and Salt-stressed Barley. Plant Molecular Biology 48: 551-573.

Pellegrineschi, A., L.M. Noguera, B. Skovmand *et al.* 2002. Identification of highly transformable wheat genotypes for mass production of fertile transgenic plants. Genome 45(2): 421-30.

Russell, J.R., A. Booth, J.D. Fuller *et al.* 2003. Patterns of polymorphism detected in the chloroplast and nuclear genomes of barley landraces sampled from Syria and Jordan. Theor Appl Genet. 107: 413-21.

Sasanuma, T., K. Chabane, Endo *et al.* 2002. Genetic diversity of wheat wild relatives in the Near East detected by AFLP. Euphytica 127(1): 81-93.

Sasanuma, T., K. Chabane, Endo *et al.* 2004. Characterization of genetic variation in and phylogenetic relationships among diploid Aegilops species by AFLP: incongruity of chloroplast and nuclear data. Theor Appl Genet.108(4): 612-8.

Seki, M., M. Narusaka, H. Abe *et al.* 2001. Monitoring the expression pattern of 1300 Arabidopsis genes under drought and cold stresses by using a full-length cDNA microarray. Plant Cell 13, 61–72.

Somers, D., D.A. Samac, P.M. Olhoft. 2003. Recent Advances in Legume Transformation. Plant Physiol. 131: 892-899.

Udupa, S.M., L.D. Robertson, F. Weigand *et al.* 1999. Allelic variation at (TAA) in microsatellite loci in a world collection of chickpea (Cicer arietinum L) germplasm. Mol.Gen.Genet. 261:354-63.

Chapter 9

Plant Biotechnology in Developing Countries: Opportunities and Constraints

Malcolm Elliott, Leila G. Rubia, Latha Rangan, Miroslav Kaminek, and Anatole Krattiger

Introduction

The Green Revolution enabled global food production to increase 2.8% annually between 1966 and 1990, while the world's population increased 2.2% annually (Kendall and Pimentel, 1994). These trends have since been reversed. Between 1990 and 1997, the annual population increase was 1.7%, while food production increased 1.2% per year (Borlaug, 1997). If humankind fails to deliver the "Evergreen Revolution" then very serious food shortages are likely to occur in this century (Swaminathan, 2000). The developing countries are currently facing poverty, environmental degradation, and conflict, each of which affects food security (Lele, 2003).

Some 1.2 billion people are absolutely poor (they earn less than US$1 a day), and another 2 billion people are only marginally better off (World Bank, 2000). It is predicted that the world's population will increase from its present level of 6 billion to 8 billion by 2025 (Pimentel et al., 1994). This supreme challenge to gobal food security will be enhanced by rising expectations which will put even more pressure on food grains. As people move into higher income brackets they are likely to consume more livestock products, such as meat, milk and eggs. These products are produced at the expense of higher consumption levels of feed grains. Thus, population increases and changes in eating habits are likely to increase food grain requirements by 70% by 2025 (Leisinger et al., 2002). However, there is little additional land available for food production (Borlaug, 2004).

Poor people in the developing countries derive their livelihoods from agriculture or, at least, are heavily dependent on agriculture. The prospect of satisfying their needs is challenged by the fact urbanization and industrialization are causing some of the best agricultural lands to be taken out of production while water is being withdrawn from agriculture for domestic and industrial purposes, labor is

shifting from agriculture to industry, traditional sources of energy are likely to be constrained, and concerns about the overuse and misuse of chemicals in agriculture are being expressed with great passion (Sasson and Elliott, 2004).. Thus, humankind will need to produce more food from less land, with less water, less labor, less fuel and fewer applications of agrochemicals. To meet this challenge, we need to use the tools of plant biotechnology to facilitate the production of crop varieties with higher yield potential, with resistance to diseases and insects, and with tolerance to stresses such as drought, salinity and unfavorable temperatures.

Tools of Plant Biotechnology

In 1953, Watson and Crick established the structure of deoxyribonucleic acid (DNA) and prepared the way for the era of molecular biology. Watson (2003) described the ways in which genomics, proteomics, and bioinformatics have paved the way towards making biological systems more efficient and precise. A wide array of plant biotechnology tools is available for development of better crop varieties, and the merit of molecular approaches to crop improvement has been recognized by farmers in industrial and developing countries.

The revelation of the complete genome sequences of *Arabidopsis* and rice has profound implications for agriculture. It will enable detailed studies on genetic organization in plants that will underpin improvements in crop yields and quality, disease and drought resistance, ripening and spoilage.

High input (industrial style) agriculture incurs high costs for agrochemicals and water. Biotechnology-based solutions could reduce the demands for these resources and reduce the deleterious effects of diseases and weeds, thus promoting sustainable agricultural production (Sasson and Elliott, 2004). Biotechnology is a vital tool for addressing the problems of hunger, malnutrition and disease in developing countries (Khush and Ma, 2004).

Status of Plant Biotechnology Products in the Pipeline

Three generations of crops are currently in the plant biotechnology pipeline (Figure 9.1, after Coburn, 2004). The first generation of crops features agronomic traits that make them easier for farmers to grow, or better adapted to modern agricultural systems. The second generation of crops carries quality traits that have an effect on the nutritional value of food and feed and the third generation of crops uses plants as production systems for pharmaceuticals and renewable industrial compounds (Coburn, 2004).

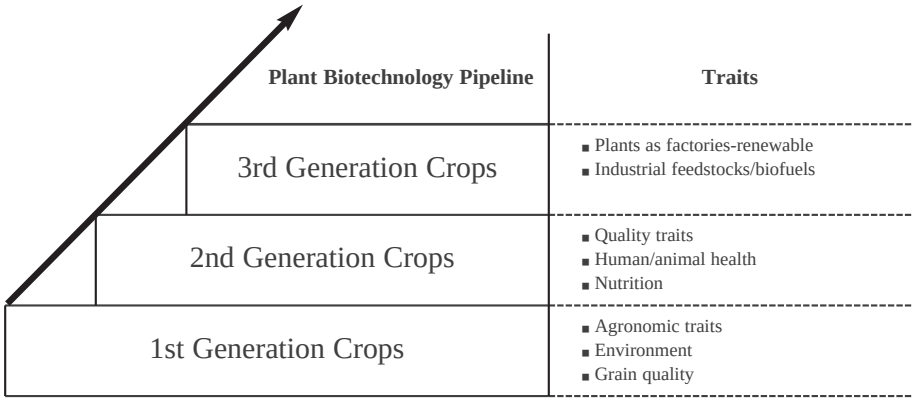


Figure 9.1. The plant biotechnology pipeline (modified from Coburn, 2004)

Global Status of Transgenic Crops

Farmers in industrial and developing countries have rapidly adopted transgenic crops because they recognized their significant benefits in terms of increased yields, decreased requirement for agrochemicals, and improved cost-effectiveness. The global area of transgenic crops increased from 1.7 million hectares in 1996 to 67.7 million hectares in 2003, growing to 81 million hectares in 2004, with an increasing proportion grown in developing countries (James, 2003, 2004). Of the 67.7 million hectares planted in 2003, about 20 million hectares were grown in developing countries where massive increases in the use of transgenic crops are continuing to occur. The percentage increase in the area of genetically modified (GM) crops was more than twice as high (28%) in developing countries as in the industrial countries. This increase in the global area of transgenic crops reflects farmer satisfaction with GM plants and products.

In 2003, transgenic crops were grown in 18 countries distributed across six continents (Asia, Africa, Europe, Latin America, North America, and Oceania), occupied by almost one-half of the world's population (James, 2003). The top 10 countries, growing 50,000 hectares or more of GM crops, were the USA followed by Argentina, Canada, Brazil, China, South Africa, Australia, India, Romania and Uruguay. But the top six of the leading countries grew 99% of the global transgenic crop area, which shows the increasing participation of these leading GM countries. The USA grows 42.8 million hectares (63.36% of the total global area), followed by Argentina with 13.9 million hectares (20.58%), Canada with 4.4 million hectares (6.51%), Brazil with 3 million hectares (4.44%), China with 2.8 million hectares (4.15%) and South Africa with 0.4 million hectares (0.59%) (James, 2003).

Transgenic crops are planted on less than 0.2 million hectares in Romania, Uruguay, Spain, Germany, Mexico, Philippines, Colombia, Bulgaria, Honduras and Indonesia. In spite of the continuing controversy about GM crops, the area planted with GM crops and the number of farmers growing GM crops has increased at a double-digit rate every year. In 2004, the area of GM crops increased by 20% over 2003 (James, 2004).

Eight transgenic crops dominate commercial plantings (James, 2003). Herbicide-tolerant soybean is the most abundant transgenic crop, grown in seven countries (USA, Argentina, Canada, Mexico, Romania, Uruguay, and South Africa). Herbicide-tolerant soybean is planted on 41.4 million hectares (62% of the total global area of transgenics) in 2003. Bt maize is the second most prevalent GM crop, planted in 9.1 million hectares (13% of the total global area of transgenics) in nine countries (USA, Canada, Argentina, South Africa, Spain, Germany, Honduras, Uruguay, and Philippines). The third most widespread GM crop is herbicide-tolerant canola, which is planted on 3.6 million hectares (5% of the total global area of transgenics) in Canada and the USA. Bt/herbicide-tolerant maize, herbicide-tolerant maize and Bt cotton are grown on 3.1-3.2 million hectares (5% of the total global area of transgenics) followed by Bt/herbicide-tolerant cotton with 2.6 million hectares (4% of the total global area of transgenics) and herbicide-tolerant cotton with 1.5 million hectares (2% of the total global area of transgenics).

Many small farmers in developing countries are adopting GM technology, but globally the share of GM crops planted by developing countries is less than 2% of the total cropped area. The farmers' share in total benefits is thought to be as high as 88% from GM crops in China and 86% from GM crops in Mexico compared to a farmers' share of 45% in the US cotton industry (Traxler, 2002). The increase in investment in modern biotechnology by the public sectors of large developing countries (especially China, India, and Brazil) enables widespread experimentation with GM technology within their public sector research organizations. Thus, modern biotechnology offers tremendous potential to address the challenges of providing food security to developing countries (Sasson and Elliott, 2004).

Opportunities for Plant Biotechnology

Many small farmers in developing countries are faced with problems and constraints that plant biotechnology can help to resolve. Plant biotechnology is not a silver bullet for achieving food security, but it provides a means of reducing poverty, food insecurity, child malnutrition, and natural resource degradation in developing countries. Pinstrup-Andersen and Cohen (2000) claimed that the use of plant biotechnology tools, GM crops, and their products in the developing countries can:

- Reduce poverty, food insecurity, child malnutrition and natural resource degradation.
- Achieve productivity gains to feed the global population.

- Introduce resistance to pests and diseases without expensive purchased inputs.
- Increase the tolerance of crops to adverse weather and soil conditions.
- Enhance the nutritional value and quality of food.
- Improve the durability of products during harvesting and/or shipping.
- Decrease reliance on pesticides.
- Reduce use of herbicides and labor.
- Improve the health of many people.
- Lower farm production costs.
- Decrease the costs of protecting farmers' crops.
- Provide benefits to the environment
- Offer cost-effective solutions to micronutrient malnutrition by using crops rich in vitamin A and iron.
- Increase yield and productivity in food production.
- Decrease the need to cultivate new lands.
- Protect fragile ecosystems.
- Conserve biodiversity.

Scientists in developing countries need to deploy the techniques of biotechnology for DNA sequencing; DNA fingerprinting; transformation of crops for herbicide, insect, disease, and drought resistance; improvement of the nutritional quality of food; characterization and enhancement of germplasm; and marker-assisted selection (Lele et al., 2003). The further benefits of using plant biotechnology are precision, lower costs of research, improved incomes, improved quality of life, reduced consumer prices, and delivery of a broad range of biotechnology products (Watson, 2003).

Particular mention must be made of two tools of crop biotechnology that can benefit crop enhancement strategies.

Marker-Assisted Selection (MAS)

Marker-assisted selection has the potential to improve traits that are difficult to address by conventional breeding procedures. Progress in MAS breeding is being achieved mainly in the area of disease resistance. Progeny have been obtained from crosses with parents in various crop species that carry resistance genes. The aim was to pyramid resistances against diseases. MAS is suitable for such specific breeding aims as:

- Gene pyramiding (monogenic and polygenic resistance).
- The identification of homozygous lines.
- Early screening of traits that can usually only be evaluated at a late developmental stage (mildew, fruit quality, and fruiting behavior).

‘Clean Gene’ Technology

Transgenic technologies promise to enhance research in plant molecular genetics and to facilitate crop improvement strategies with colossal benefits for humankind. Important limitations must, however, be recognized in the uncontrolled factors affecting the integration and behavior of transgenes. Strategies to control transgene integration and to limit unwanted or multiply-integrated DNA sequences are central to the development of plant transformation technologies. Among these, the production of marker-free transgenic plants is particularly important.

Research funded by the UK Department for International Development (DFID) at the Norman Borlaug Institute (NBI) and the John Innes Centre (JIC) has been successful in establishing procedures for producing transgenic crops that are free of unwanted selectable marker genes (such as antibiotic resistance genes). The crops also contain simple transgenic loci. This overcomes a constraint on the employment of genetic engineering that has been imposed as a consequence of extreme public reaction to the perceived dangers of inclusion of antibiotic resistance genes in crops. It must be stressed that there is absolutely no evidence of such risks, but there is no need to retain such genes in the transgenic crops after the selection process has been completed. They should be eliminated before genetically enhanced crops are grown commercially.

Benefits to Developing Countries

An integrated approach to Mendelian and molecular breeding will be most effective in bringing new technology to the benefit of humankind. Many poor farmers and consumers in developing countries are already gaining benefits from using plant biotechnology and its products (Toenniessen et al., 2003). The use of Bt cotton provides millions of farmers with higher yields, decreased insecticide costs and fewer health risks. Huang et al. (2003) reported that GM technologies provide huge benefits to farmers because of time-saving gains, higher yields and decreased chemical pesticide inputs. In Argentina, the price of herbicide-resistant soya beans decreased because of the reduced need for pesticides. In China, the use of Bt cotton decreased the frequency of pesticide spraying, making the price of Bt cotton cheaper than non-Bt cotton. In Mexico and South Africa, there are lower farm costs and higher yields from Bt cotton.

Comparative studies of GM crops produced via modern biotechnology in Mexico and the USA (Traxler, 2002) and in China (Pray et al., 2003) have come to important conclusions. The yield of Bt cotton in Mexico (Traxler, 2002), China (Pray et al., 2003) and in India (Qaim and Zilberman, 2003) and the yield of Bt maize in South Africa (Ismael et al., 2001) are higher compared with conventional varieties. Traxler (2002) estimated the incremental profits per hectare of Bt cotton production

relative to conventional varieties across several countries. He noted that there was substantial variation in the level of profits between countries, but concluded that the farm production costs for Bt plants are lower due to the reduced use of pesticides and labor. Pray et al. (2003) reported that the main benefits of using GM cotton in China for the past five years were the reduced application of chemical inputs and lower requirement for labor, which led to improved health and well-being of many people. More than 4 million farmers planted Bt cotton in the Yellow River Delta with a substantial increase in cotton production compared with non-GM cotton. Bt crops reduced pesticide use, reduced farm costs, and reduced the incidence of insecticide poisoning. In 2003, seven million farmers benefited from GM crops compared with six million farmers in 2002. More than 85% of these seven million farmers were resource-poor farmers who planted Bt cotton, primarily in nine provinces of China and the Makhathini Flats in KwaZulu Natal Province in South Africa (James, 2003).

Constraints on the Exploitation of Plant Biotechnology

Many developing countries have the potential to break through the crop yield ceiling and overcome the deadlock in crop production. Unfortunately, as Norman Borlaug (personal communication) has frequently remarked, a large gap still exists between potential and actual yields even with the technologies available. The gap is widened many fold because of the following factors:

1. The decrease in funds from donors for international public research

Insufficient funding/financial support for basic and applied research in modern biotechnology is a problem in many developing countries. Lending to support agricultural research in developing countries has decreased precipitously since the early 1990s. Currently, only an estimated US$50 million of the World Bank's agricultural loans go to biotechnology (Lele et al., 2003).

The Consultative Group on International Agricultural Research (CGIAR) has 16 centers around the world. They have played a vital role in helping millions of poor people to attain food and livelihood security, but CGIAR funding has decreased in real terms from 1994 to 2002. The share of restricted funding to the CGIAR Centers has increased from 36% to 57% in 2002. CGIAR spends only US$325 million per year on agricultural research compared with US$10 billion by the private sector.

2. Lack of government policies, programs and support for plant biotechnology

Small and/or low-income developing countries, particularly in Africa, do not have the capacity to invest in biotechnology research to support crops with limited market prospects but that are of substantial interest to poor farmers with low risk tolerance. This is evident from the fact that the global private sector agricultural research investment in developing countries is only US$0.7 billion compared to US$10.8 billion in industrial countries.

- Political support for public sector funding for research has recently been lacking (Paarlberg, 2002).
- Over the past decade there has been some advocacy of the need for a pro-poor, pro-nature, and pro-women bias in the development and dissemination of modern biotechnology (Swaminathan, 1991). Agricultural biotechnology research is one area that could have differential and dramatic impacts on poverty alleviation. A wide range of approaches to biotechnological enhancement of crop yields in low-income, food-deficit countries is already available or well advanced in the research pipeline. However, the current lack of focused public sector support for pro-poor agricultural biotechnology will make it unlikely that poor farmers will have access to such technology in the near future.
- Yields can be increased, provided political stability is restored, bureaucracies are reduced, and the researchers and extension workers are able to devote more energy to putting science and technology to work at the farm level.
- Within the broader agricultural research community there is a lack of priority-setting mechanisms and cost-benefit analyses to determine which available technological approaches may be the most suitable within particular time-frames for addressing the prioritized agronomic needs of the particular groups of farmers (Brenner, 1996). Farmer participation will enable assessments to determine research priorities prior to initiation of research and development.
- Plant biotechnology is failing to empower poor farmers or improve their livelihoods in many Indian states because there is no linkage between farmers (participatory researchers), extension workers, and plant biotechnologists. Furthermore, there is no integration between conventional breeding and agricultural improvement approaches. Biotechnology is here to complement conventional breeding strategies but not to replace them.

3. Extensive biosafety regulations

There are extensive biosafety regulations for GM crops. They require hundreds of individual safety tests that are often duplicative and hugely unnecessary for ensuring consumer safety (Khush and Ma, 2004). These overcautious rules lead to hyper-

inflated research and development costs, making it more difficult for poorer countries to share in the immense benefits of biotechnology.

The politicization and blockage of national biosafety screening processes are crucial factors that limit the availability of GM crops for developing countries (Paarlberg, 2002). Almost all major developing countries now have GMO biosafety regulations and/or guidelines in place, and most of the countries have constituted national biosafety committees to review GM crop applications for environmental and commercial release. However, only a few approvals have been given to date. At present only South Africa, in the whole continent of Africa, has given commercial planting approval for any GM crop (maize and cotton). In Asia, only China, India, and Indonesia have given significant commercial GM crop planting approvals for cotton. In most of the developing countries in Asia and Africa, it is still technically illegal for farmers to plant any GM food or feed crops because the national biosafety regulators have denied approvals.

It is important to consider the real reasons for the refusal of biosafety approval. The slow approvals in some cases have resulted in part from limited scientific and administrative capacity to conduct the elaborate and expensive case by case biosafety screenings. Donors can insist upon such screenings as a condition for financial or technical assistance (Paarlberg, 2002). In other countries, such as Brazil and India, the approval process has been blocked or slowed by lawsuits, media campaigns, and direct political actions undertaken by well-funded anti-GMO nongovernmental organization (NGO) activists. The approval process in developing countries has often been delayed because of the increasing fear that export sales to Europe and Japan might be lost if the planting of GM crops (especially food and feed crops) is permitted. Thus, Chinese officials announced in April 2001 that new GM commercial releases, especially of food crops, are under a temporary freeze because of their concern about international consumer resistance to GM foods. Labeling capacity is also weak in developing countries, and it is too costly to try to segregate farm products into separate GM or non-GM marketing channels, so the people opt to remain entirely "GM free."

In addition, the implementation of the Cartagena Protocol on Biosafety, without immediate action by the world's public research community, is prone to increase even further the regulatory burden in developing countries. For example, the first Meeting of the Parties to the Cartagena Protocol was attended by more than 100 NGO representatives "with an antiscience and antitechnology agenda," and without "representation of the scientific community as a stakeholder group" (De Greef, 2004). Similarly, the debates and working groups within the Protocol all focus on the risks of biotechnology, without considering the tremendous current and potential benefits. This has led to negotiations related to Liability and Redress, with the clear possibility of bringing about regulations that might be suitable for large, private sector developers but that ignore the needs of public researchers and public institutions. De Greef (2004) thus calls for a clearer analysis of the economic, human, and environmental costs of the regulatory options being considered by the Protocol,

and for a voice to raise the concerns and needs of the scientific community and the public research sector.

4. Intellectual property rights (IPRs)

At present, IPRs are seen as a key barrier to the delivery of the benefits of GM crops into the hands of poor farmers in developing countries (Paarlberg, 2002). Weak IPR protection and infringement exist in developing countries. Fragmented ownership of intellectual property is a huge problem. For example, in Golden Rice , 40-70 patents and a set of material transfer agreements (MTAs) needed to be negotiated (Kryder et al., 2000). Nevertheless, whereas that number of intellectual property constraints for one single product seems extraordinarily large, it took a mere three months to negotiate one master license for Golden Rice which, since then, has been signed by well over 30 public institutions in Asia. It must be emphasized that the development of Golden Rice for the benefit of developing countries has not been delayed as a result. However, resolving IPR constraints does constitute an expense that may be prohibitively high for under-funded public research institutions.

The other problems include information on patents, the expensive transaction costs of negotiations, the variable and confused IPR regulatory environment among countries, reduced freedom to operate, and increased costs of converting research into commercial products (Nottenberg et al., 2003; Cohen and Paarlberg, 2002; Graff and Zilberman, 2001; Lele, 2003).

5. Seed distribution systems

Most agricultural products, because they are living organisms, have the ability to reproduce themselves. With the inclusion of transgenic components in many recently released improved agricultural products, they pass along their biotech components, whether the components are IPR-protected or not, from generation to generation. Biotechnology has thus prompted the invention of new seed marketing schemes and is calling into question the historical patterns of seed distribution. Nowhere is this shift expected to be more dramatic than among the least developed countries. The expensive proprietary technologies, it is feared in many quarters, will become public property in many such countries. Paradoxically, these countries are also the ones that potentially could benefit most from the technological advancements that are protected by IPR, both from a socioeconomic and environmental perspective. Thus investments need to be increased significantly in improving seed production and distribution mechanisms to allow developing country farmers to benefit from a range of potential suppliers.

6. Impact of the new EU regulation on release of GM food and feed in developing countries

Many authorities in developing countries have adopted a go-slow approach toward plant biotechnology, and they are delaying the planting of any GM food or feed crops for fear of losing their access to key export markets in the industrial world, particularly Europe and Japan (Paarlberg, 2002). The consumer and policy resistance toward GM foods are barriers to placing GM seeds in the hands of farmers in developing countries.

Although GM cotton is planted in some developing countries, farmers in many poorer developing countries today have still not planted GM food or feed crops (Paarlberg, 2002). The government authorities in many of these countries have not yet given the farmers official permission to plant any GM food or feed crops because, they claim, of "precautionary concerns" about biological safety. The main reason seems to be the fear that consumers in high-income countries such as in Europe and Japan will shun imports from any country that begins planting GM varieties.

7. Trade policies

Since October 2002, the EU's implementation of its stringent labeling and traceability policy for GM foods has ratcheted up the cost of gaining legal access to the EU market for exporters in countries such as the USA, Argentina, and Canada, where GM soybean, corn, or canola varieties are currently being planted (Paarlberg, 2002). The EU policy requires exporters to label the GM content of all foods, including processed foods in which the GM content is no longer detectable through physical testing. The implication of this is that separate varieties of GM crops must be physically segregated from non-GM crops and from each other at every step of the production, transport, and processing chain. Because of this, developing countries have responded by halting the export of GM foods and feeds. Some developing countries, such as China, India, and Indonesia, are moving ahead with GM cotton but holding back on GM food and feed crops because the concerns about exports are driving the technology approval process.

8. The campaigns of anti-GMO groups

There is an intense debate, in certain industrial countries, about the value and safety of GMOs. Consumer fears are fuelled by a variety of concerns such as unfamiliarity, lack of reliable information about regulatory safeguards, a steady stream of negative opinions in the news media, opposition by activist groups, growing mistrust of industry, and a general lack of awareness of how our food production systems have evolved over time (Khush and Ma, 2004). This situation continues in spite of the fact

that there is absolutely no evidence that plant biotechnology creates any new environmental or public health risks (ICSU, 2003).

9. Public perception of transgenic crops and products

Many things have been written about the perceptions of transgenic crops and their products. Some people present it as an exciting opportunity to use modern biological techniques to improve the quality of agricultural plants and their products, whereas others see it as an insidious attempt to extend the power of multinational companies, hence threatening the well-being of subsistence farmers and the ecology of fragile ecosystems (Dunwell, 2002). The increase in opposition, particularly to the commercialization of GM products in Europe, is affected by the occurrence of major health crises such as the mad cow disease outbreaks in the UK. The disasters were not, of course, related to GM technology, but they have created a distrust of science, public regulation, and expertise. This has been the key difference between public attitudes in the USA and Europe. The mass media have been prone to emphasize negative publicity about public health or environmental problems. As a result of these effects, GM crops have become a very difficult issue for policymakers. The high level of opposition is clearly linked to the lack of public understanding of plant biotechnology. Traditional plant breeding methods are perceived to be associated with preservation and protection of "nature," whereas biotechnology is considered to have a negative effect on "nature." Hence, the use of GMOs in crop improvement is perceived negatively. The political consequences of these negative perceptions are serious in the UK and in other industrial countries. Delays in GM acceptance in Europe have led to the retention of high input and less "environmentally friendly" farming practices (Coburn, 2004).

Conclusion

Malthus predicted 200 years ago that human population growth would exceed humanity's capacity to produce food. The tools of plant biotechnology have been used increasingly in crop improvement, and they are available to facilitate the provision of enough food to satisfy the growing world population (Borlaug, 2004). These tools can offset the negative consequences of agricultural intensification and decrease environmental degradation, but if further progress is to be made, the polarized views and extended debate over the cultivation of GM crops will need to be set aside in favor of decision making and action. This action requires political will. Scientists, economists, politicians, farmers, consumers, and conservationists need to work together to use all available means, including plant biotechnology, to meet the needs of the rapidly growing world population, while preventing environmental

degradation. And as with any new technology, it is necessary to proceed prudently and cautiously (Coburn, 2004).

Plant biotechnology is a useful tool for crop improvement, which could be hugely important for economic development in poor developing countries that rely on agriculture for their livelihood (Khush and Ma, 2003). The new technology can help agriculture to be more productive so that real food security enables labor and resources to be freed for use in other areas of economic growth. Although there is considerable appreciation of the merits of crop biotechnology, the developing countries are hesitating to move quickly toward releasing GM crops for commercial planting because of the considerations of trade policy, consumer preferences, and claims of risks to the environment.

Plant biotechnology tools, transgenic crops, and GM products are available to developing countries. However, these countries need to deal with increasingly complex trade issues and consumer concerns about health and the environment if they are to increase support from the private sector (Lele, 2003). Global collective action is needed to utilize communications and information technologies, reduce research and transaction costs for developing countries, standardize regulations for biosafety and food safety, narrow the scientific, human, and information gaps, and increase consumer confidence (Lele, 2003). Furthermore, increased public sector funding for research in developing countries and generous funding by donor countries can help extend useful applications of plant biotechnology to poor farmers in the developing countries (Paarlberg, 2002). Plant biotechnology is a powerful tool to reduce poverty and attain food, fiber, and feed security for poor people and small farmers in developing countries.

References

Borlaug, N.E. 1997. Feeding a world of 10 billion people: The miracle ahead. Plant Tissue Culture and Biotechnology 3, 119-127.

Borlaug, N.E. 2004. Feeding a world of 10 billion people: our 21st century challenge. In: Scanes, C.G. and Miranowski, J.A.(eds) Perspectives in World Food and Agriculture 2004. Iowa State Press, pp. 31-55.

Brenner, C. 1996. Integrating biotechnology in agriculture: incentives, constraints and country experiences. OECD Development Centre, Paris, France.

Coburn, A. 2004. Commercial plant breeding: what is in the biotech pipeline? Journal of Commercial Biotechnology 10(3): 209-223.

Cohen, J., and R. Paarlberg. 2002. Explaining restricted approval and availability of GM crops in developing countries. AgBiotechNet 4:1-6.

De Greef, W. 2004. The Cartagena Protocol and the future of agbiotech. Nature Biotechnology 22, 811-812.

Dunwell, J. 2002. Future prospects for transgenic crops. Phytochemistry Reviews. 1:1-12.

Graff, G., and D. Zilberman. 2001. An intellectual property clearing house for agricultural biotechnology. Nature Biotechnology 19:1179-1180.

Huang, J., C. Pray, and S. Rozelle. 2003. Enhancing the crops to feed the poor. Nature 418:678-684.

ICSU. 2003. New Genetics, Food and Agriculture: Scientific Discoveries–Societal Dilemmas. International Council for Science, Paris. 56 p.

Ismael, Y., R. Bennett, and S. Morse. 2001. Biotechnology in Africa: the adoption and economic impacts of Bt. cotton in the Makhthini flats. Paper presented to the AfricaBioConference, Biotechnology Conference for Sub-Saharan Africa, Johannesburg, South Africa.

James, C. 2002. Global Status of Commercialized Transgenic Crops: 2002. ISAAA Brief No. 27, ISAAA, Ithaca, N.Y. (URL: http://www.isaaa.org/).

James, C. 2003. Preview: Global Status of Commercialized Transgenic Crops: 2003. ISAAA Briefs No. 30, ISAAA, Ithaca, N.Y. pp. 1-25 (URL: http://www.isaaa.org/).

James, C. 2004. Preview: Global Status of Commercialized Biotech/GM Crops: 2004. ISAAA Briefs No. 32, ISAAA, Ithaca, N.Y. 43p.

Juma, C. 2001. Appropriate technology for sustainable food security. A 2020 Vision for Food, Agriculture and the Environment, IFPRI Focus.

Kendall, H.W., and D. Pimentel. 1994. Constraints on the expansion of the global food supply. Ambio 23: 198-205.

Khush, G., and J. Ma. 2004. Crop biotechnology for developing countries: opportunity and duty. In: Christou, P., and Klee, H.(eds). Handbook of Plant Biotechnology. John Wiley and Sons, Chichester, England, pp.1313-1320.

Kryder, R.D., S. Kowalski, and A.F. Krattiger. 2000. The intellectual and technical property components of pro-Vitamin A rice (GoldenRice™): A Preliminary Freedom-to-Operate Review. ISAAA Briefs No. 20, ISAAA, Ithaca, N.Y. pp74.

Leisinger, K.M. 1999. Ensuring food security, protecting the environment, and reducing poverty in developing countries: Can biotechnology help? International Conference on Biotechnology CGIAR–National Academy of Sciences, The World Bank, Washington, D.C. 21-22 October 1999. p. 173-180.

Leisinger, K.M, C. Schmitt, and L. Pandya. 2002. Six billion and counting, population and food security in the 21st Century. Washington, D.C.: International Food Policy Research Institute.

Lele U. 2003. Biotechnology: opportunities and challenges for developing countries. Amer. J. Agr. Econ. 85(5): 1119-1125.

Lele, U., C. Barrett, C.K. Eicher, B. Gardner, C. Gerrard, L. Kelly, W. Lesser, K. Perkins, S. Rana, M. Rukuni, and Speilman. 2003. The CGIAR at 31: An Independent MetaEvaluation of the Consultative Group on International Agricultural Research. Operations Evaluation Department, The World Bank, Washington, D.C., 9 May 2003.

Nottenberg, C., P. Pardey, and D. Wright. 2003. Accessing other people's technology for non-profit research. In: Pardey, P., and Koo, B. (eds). Biotechnology and Genetic Resource Policies. International Food Policy Research Institute, Washington, D.C., Brief 4. pp.1-4.

Paarlberg, R.L. 2002. The real threat to GM crops in poor countries: consumer and policy resistance to GM foods in rich countries. Food Policy 27:247-250.

Pimentel, D., R. Harman, M. Pacenza, J. Pecarsky, and M. Pimentel. 1994. Natural resources and an optimum human population. Population and Environment 15 : 347-369.

Pinstrup-Andersen, P., and M.J. Cohen. 2000. Agricultural biotechnology: risks and opportunities for developing country food security. Int. J. Biotechnology. 2(1/2/3): 145-163.

Pray, C., J. Huang, R. Hu, and S. Rozelle. 2003. Five years of Bt cotton in China–the benefits continue. The Plant Journal 31: 423-430.

Qaim, M., and D. Zilberman. 2003. Yield effects of genetically modified crops in developing countries. Science 299: 900-902.

Sasson, A., and M.C. Elliott. 2004. Agricultural biotechnology for developing countries: a strategic overview. In: Christou, P., and Klee, H. (eds). Handbook of Plant Biotechnology. John Wiley and Sons, Chichester, England, pp.1201-1205.

Swaminathan, M.S. 1991. Reaching the unreached: biotechnology in agriculture–A dialogue. Madras: India: Macmillan India Limited.

Swaminathan, M.S. 2000. An Evergreen Revolution, Biologist 47(2): 85-89.

Toenniessen, G.H., J.C. O'Toole, and J. DeVries. 2003. Advances in plant biotechnology and its adoption in developing countries. Current Opinion 6:191-198.

Traxler, G. 2002. Biotechnology in a complete system of genetic improvement: a perspective on developed and developing countries. Presented at the Workshop on Biotechnology for Agricultural Development at the World Bank, 9 January 2002.

Watson, J. 2003. The Secret of Life. Knoft, New York.

World Bank. 2000. Attacking Poverty. World Development Report 2000/2001/ The World Bank. Washington, D.C., USA.

Chapter 10

Can Developing Countries Benefit from Agricultural Biotechnology?

Gregory Conko and C.S. Prakash

Introduction

Biotechnology is one of the latest scientific tools for developing new crop varieties to improve agricultural productivity, boost food production, reduce the use of farm chemicals, and make our food healthier. Genetically modified (GM) crops (also called transgenic, genetically engineered, or bioengineered) represent one of the fastest adopted technologies in the history of agriculture, yet they are not universally accepted because of concerns about their safety.

Food Safety Concerns in Africa

In 2002, while more than 14 million people in six drought-stricken southern African countries faced the risk of starvation, relief efforts by the UN's World Food Programme were stifled by the global "GM" food controversy. Food aid, containing kernels of bioengineered corn from the United States, was initially rejected by several governments, even though similar maize has been consumed daily by hundreds of millions in North and South America, and had been distributed by the World Food Programme throughout Africa since 1996.

This is one of the tragic consequences of global concerns about recombinant DNA technology and bioengineered crops. Although many crop varieties that are of use to resource-poor farmers in developing countries are at very early stages of development, other crop varieties that have been commercialized and consumed in countries such as Canada and the United States are being kept from farmers by policymakers skeptical of "genetic modification."

Plant and Animal Breeding Techniques

All plant and animal breeding involves–and always has involved–the intentional genetic modification of organisms. Humans have been modifying crop plants ever since farming began 10,000 years ago, when we first 'tamed' the wild plants to provide food, feed and fiber. Every crop thus is a product of repeated genetic tinkering by humans over the millennia.

As early as 1906, Luther Burbank, the noted plant breeder, said that: "We have recently advanced our knowledge of genetics to the point where we can manipulate life in a way never intended by nature. We must proceed with the utmost caution in the application of this new found knowledge." This is a quote that one might just as easily hear today regarding recombinant DNA modification.

It is not genetic modification *per se* that generates risk. Recombinant DNA-modified, conventionally modified, and unmodified plants could all prove to be invasive, harm biodiversity, or be harmful to eat. It is not the technique used to modify organisms that makes them risky. Rather risk arises from the characteristics of individual organisms, as well as how and where they are used.

That is why the use of bioengineering technology for the development of improved plant varieties has been endorsed by many scientific bodies, among others, have studied Bioengineering techniques have been studied and given a clean bill of health by the UN's Food and Agriculture Organization and World Health Organization, the UK's Royal Society, the American Medical Association, and the French Academies of Medicine and Science (ICSU, 2003).

Biotechnology and Developing Countries

The Royal Society of London, the National Academies of Science from Brazil, China, India, Mexico, and the U.S., and the Third World Academy of Science (2000), believe that bioengineering can be used to advance food security while promoting sustainable agriculture. "It is critical," declared the TWAS report, "that the potential benefits of GM technology become available to developing countries." An FAO (2000) report argued that "effective transfer of existing technologies to poor rural communities and the development of new and safe biotechnologies can greatly enhance the prospects for sustainably improving agricultural productivity today and in the future," as well as "help reduce environmental damage caused by toxic agricultural chemicals."

Today, close to 800 million people go to bed hungry, and nearly 40,000 people–half of them children–die every day due to hunger- or malnutrition-related causes. Despite commitments by industrial countries to increase international aid, Africa is expected to still have over 180 million undernourished citizens in 2030, according to the UN Millennium Task Force. Although bioengineered crops alone

will not eliminate hunger, they can provide a useful tool for addressing the many agricultural problems in Africa, Asia, Latin America, and other resource poor regions.

Genetically-modified crops have already increased crop yields and food production, and reduced the use of synthetic chemical pesticides in industrial and developing countries. These advances are critical in a world where natural resources are finite and where millions of people suffer from hunger and malnutrition. While most commercially available bioengineered plants were designed for farmers in the industrial countries, the increasing adoption of biotech varieties by farmers in developing countries over the past decade demonstrates their broader applicability.

Global Cultivation of GM Crops

Globally, bioengineered varieties are now grown on more than 80 million hectares in 18 countries, including Argentina, Australia, Brazil, Canada, China, India, Mexico, the Philippines, South Africa, and the United States (James, 2004). Nearly one-quarter of that area is farmed by nearly 6 million resource-poor farmers in developing countries. Why? Because they see many of the same benefits that farmers in industrial nations do.

The first generation of biotech crops–approximately 50 different varieties of canola, corn, cotton, potato, squash, soybean, and others–were designed to aid in protecting crops from insect pests, weeds, and plant diseases. As much as 40% of crop productivity in Africa and Asia and about 20% in the industrial countries of North America and Europe is lost to these biotic stresses, despite the use of large amounts of insecticides, herbicides, and other agricultural chemicals. Farmers in tropical areas may face different pest species than their industrial country counterparts, but both must constantly battle against these threats to their productivity.

Farmers in South Africa and the Philippines are eager to grow bioengineered corn resistant to insect pests. Chinese, Indian, and South African farmers like biotech insect-resistant cotton. Indian cotton farmers and Brazilian and Paraguayan soy growers did not wait for their governments to approve biotech varieties before they began growing them. Farmers in Brazil and Paraguay saw how well their Argentine neighbors were doing with transgenic soybean varieties and bioengineered seed to grow themselves in southern Brazil.

GM Cotton in India

During the 2002-03 growing season, some Indian cotton farmers saw no increased yield from the more expensive biotech varieties, but droughts during that year

generated harsh conditions throughout India's southern cotton belt. Many growers of conventional crop varieties also suffered unanticipated and tragic crop losses. Most of the farmers who grew bioengineered cotton in 2002 decided to plant it again in 2003, however, and total planted area grew from approximately 410,000 hectares in 2002-03 to an estimated 1.3 million hectares in 2003-04.

GM Cotton in China

There is evidence that biotech varieties have literally saved lives. In developing nations, pesticides are typically sprayed on crops by hand, exposing farm workers to severe health risks. Some 400 to 500 Chinese cotton farmers die every year from acute pesticide poisoning because, until recently, the only alternative was risking near total crop loss due to voracious insects. Researchers at the Chinese Academy of Sciences and Rutgers University in the US found that adoption of bioengineered cotton varieties in China has lowered the amount of pesticides used by more than 75%, and reduced the number of pesticide poisonings by an equivalent amount.

GM Soybean in Brazil

When the planting of bioengineered soybean was provisionally legalized in Brazil for the 2003-2004 growing season, over 50,000 farmers registered their intent to plant it. This included almost 98% of the growers in the southern-most state of Rio Grande do Sul, where the soybeans originally bred for Argentine climatic conditions grow best. What is especially noteworthy is that the government decree did not legalize commercial sales of the biotech soybean, but only authorized the planting of seed already in the possession of farmers. Thus, by registering their intent to grow the bioengineered variety, farmers were informing the government of their prior actions. The clear lesson is that, where bioengineered varieties become available, most farmers themselves are eager to try them.

Environmental Benefits of GM Crops

The productivity gains generated by bioengineered crops provide yet another important benefit: they could save millions of hectares of sensitive wildlife habitat from being converted into farmland. The loss and fragmentation of wildlife habitats caused by agricultural encroachment in regions experiencing the greatest population growth are widely recognized as among the most serious threats to biodiversity. Thus, increasing agricultural productivity is an essential environmental goal, and one that would be much easier in a world where bioengineering technology is in widespread use.

Opponents of biotechnology argue that organic farming can reduce pesticide use even more than bioengineered crops can. But organic farming practices are less productive, because there are few effective organic controls for insects, weeds, or pathogens. Converting from modern, technology-based agriculture to organic would mean either reducing global food output significantly or sacrificing undeveloped land to agriculture. Moreover, feeding the anticipated population of 8 or 9 billion people in 2050 will mean increasing food production by at least 50%.

As it is, the annual rate of increase in food production globally has dropped from 3% in the 1970s to 1% today. Additional gains from conventional breeding are certainly possible, but the maximum theoretical yields for most crop plants are being approached rapidly. Providing genuine food security must include solutions other than mere redistribution. There is simply no way for organic farming to feed a global population of 9 billion people without having to bring substantially more land into agricultural use. Dramatically improving crop yields will prove to be an essential environmental and humanitarian goal.

We have already realized significant environmental benefits from the biotech crops currently being grown, including a reduction in pesticide use of 20 million kg in the US alone. Carpenter *et al.,* (2002) found that rDNA-modified crops in the US promote the adoption of conservation tillage practices, resulting in many other important environmental benefits, that included 37 million tons of topsoil preserved; an 85% reduction in greenhouse gas emissions from farm machinery; a 70% reduction in herbicide runoff; a 90% decrease in soil erosion; and a saving of 3.5-6.2 liters of fuel per hectare.

Future GM Crops for the Developing World

Although the first generation of bioengineered crops was not designed with farmers in developing countries in mind, these varieties are highly adaptable. Examples of the varieties that are now being designed specifically for resource-poor farmers include virus-resistant cassava, insect-resistant rice, and insect-resistant pigeon pea. Chinese scientists, leaders in the development of bioengineered and conventional rice, have been urging their government to approve commercialization of their biotech rice varieties that have been thoroughly tested and ready for market for several years.

The next generation of products, now in research labs and field trial plots, includes crops designed to tolerate climatic stresses such as extremes of heat, cold, and drought, as well as crops designed to grow better in poor tropical soils high in acidity or alkalinity, or contaminated with mineral salts. A Mexican research group has shown that tropical crops can be modified using rDNA technology to improve tolerance to acidic soils, significantly increasing the productivity of corn, rice, and papaya. These traits for greater tolerance to adverse environmental conditions would be tremendously advantageous to poor farmers in developing countries, especially in Africa.

Africa did not benefit from the Green Revolution as much as Asia and Latin America. Much of the African dry lands have little rainfall and no potential for irrigation, both of which play essential roles in productivity success stories for crops such as Asian rice. The remoteness of many African villages and the poor transportation infrastructure in landlocked African countries make it difficult for African farmers to obtain agricultural chemical inputs such as fertilizers, insecticides, and herbicides–even if they could afford them. However, by packaging technological inputs within seeds, biotechnology can provide the same, or better, productivity advantages as chemical or mechanical inputs, but in a much more user-friendly manner. Farmers would be able to control insect pests, viral or bacterial pathogens, extremes of heat or drought, and poor soil quality, just by planting these crops.

"Golden Rice," with added beta carotene, is one of many examples of bioengineered crops with improved nutritional content. Indian scientists have recently announced development of a new high-protein potato variety available for commercial cultivation. Another team of Indian scientists is developing an improved mustard variety with enhanced beta-carotene in its oil. Tuskegee University is enhancing the level of dietary protein in sweet potato, a common staple crop in sub-Saharan Africa. Researchers are also developing varieties of cassava, rice, and corn that more efficiently absorb trace metals and micronutrients from the soil, have enhanced starch quality, and contain more beta-carotene and other beneficial vitamins and minerals.

Addressing Public Concerns

Ultimately, while no assurance of perfect safety can be made, breeders know far more about the genetic makeup, product characteristics, and safety of every modern bioengineered crop than those of any conventional variety ever marketed. Breeders know exactly what new genetic material has been introduced. They can identify where the transferred genes have been inserted into the new plant. They can test to ensure that transferred genes are working properly and that the nutritional elements of the food have been unchanged. None of these safety assurances have ever before been made with conventional breeding techniques. We have always lived with food risks. But modern genetic technology makes it increasingly easier to reduce those risks.

Societal anxiety over the new tools for genetic modification is, in some ways, understandable. This concern is fueled by a variety of causes, including consumer unfamiliarity, lack of reliable information on the current safeguards in place, negative opinion in the media, opposition by activist groups, growing mistrust of industry, and a general lack of awareness of how our food production system has evolved. But saying that public apprehension over biotechnology is understandable is not the same as saying that it is valid. With more than 30 years of experience using

recombinant DNA technology, and nearly 20 years of pre-commercial and commercial experience with bioengineered crop plants, we can be confident that it is one of the most important and safe technologies in the plant breeder's toolbox. It would be a shame to deny biotechnology's fruits to those who are most in need of its benefits.

References

Carpenter, Janet, Allan Felsot, Timothy Goode, Michael Hammig, David Onstad, and Sujatha Sankula, 2002. Comparative Environmental Impacts of Biotechnology-derived and Traditional Soybean, Corn and Cotton Crops. Ames, Iowa: Council on Agricultural Science and Technology.

FAO. 2004. The State of Food and Agriculture 2003-2004–Agricultural Biotechnology: Meeting the needs of the poor? Rome: Food and Agriculture Organization of the United Nations.

ICSU. 2003. New Genetics, Food and Agriculture: Scientific Discoveries–Societal Dilemmas. Paris: International Council for Science. 56p.

James, Clive. 2003. Preview–Global review of Commercialized Transgenic Crops: 2003. ISAAA Briefs No. 30. Ithaca, N.Y.: International Service for the Acquisition of Agri-Biotech Applications.

James, Clive. 2004. Preview–Global Status of Commercialized Biotech/GM Crops: 2004. ISAAA Briefs No. 32. Ithaca, N.Y.: International Service for the Acquisition of Agri-Biotech Applications.

Royal Society of London, the U.S. National Academy of Sciences, the Brazilian Academy of Sciences, the Chinese Academy of Sciences, the Indian National Science Academy, the Mexican Academy of Sciences and the Third World Academy of Sciences. 2000. Transgenic Plants And World Agriculture. Washington, D.C.: National Academy Press.

Chapter 11

Biotechnology in Agriculture: Partnerships for Success

James Peacock

Introduction

Gone are the days when the traditional pattern of research was an individual scientist working in a laboratory, publishing results in a scientific journal and then, usually at low frequency, the results being picked up for commercial development. There was little contact between the researcher and the commercial enterprise. This is no longer a viable scenario in science.

Even in the research there is a need for coordinated work in a number of disciplines. There are some sophisticated and powerful technologies available to the biotechnology researcher, but in general the researcher must work in a team if discoveries are to be made in a reasonable time frame. The team has to extend along the business chain. Some researchers have regarded partnerships to have high nuisance value but most, having experienced them, agree the interactions between the different groups provide new knowledge, new approaches, and momentum to a project. I am convinced that partnerships are the only way in which biotechnology, modern biology, will be able to be of major assistance to production systems in developing countries.

Commercial Alliances in Cotton

We have formed different types of alliances between our CSIRO research group in Australia and various organizations in Australia and worldwide. These partnerships are not addressing developing country agriculture, but the principles apply to all countries. Australia has one of the most efficient cotton production systems in the world, with the highest yields and highest quality lint. This ensures a competitive position in the global markets. The industry has been criticized for its dependence on chemical insecticides, and a few years ago it became clear that the existence of the

industry was under threat because of the build-up of resistance in the pest insects.It became clear that gene technologies were likely to play a valuable role.

Transgenic insect-proof cotton was introduced in Australia in 1998. It has been remarkably successful. The general community has appreciated that the introduction of the insect-proofing gene has resulted in a large reduction in the use of chemical insecticides: 60% less aerial spraying. With the introduction of a two-gene system of insect-proofing, the expectation for the 2004 season is that insecticide use in the cotton industry will be down by over 80%. This is a big environmental plus. Additionally, farmers have increased profits through lower input costs, and for the first time in Australia we are now able to practise integrated pest management, which is a major plank for the development of a stable, sustainable agricultural system.

The research group in CSIRO formed partnerships that led to the success of transgenic cotton. The Cotton R&D Corporation (CRDC) has supported the breeding program in CSIRO. These cultivars are protected by Plant Breeders Rights. Seed is multiplied by Cotton Seed Distributors (CSD), a nonprofit company formed by the industry, with the aim of providing quality planting seed to the growers at the lowest possible cost. CSD has the exclusive rights to sell CSIRO varieties in Australia. The partnership between the R&D Corporation, the seed company, the growers, and the researchers has been supported by an active communication program at all stages. This has provided valuable feedback to the breeders in regard to their objectives. CSIRO and CRDC receive royalties from the sale of seed, and these funds are reinvested in research. CSD reinvest their profits from seed sales into facilities and infrastructure to provide improvements for the production industry.

The partnership is relatively simple but effective. It became slightly more complex with the introduction of transgenic cotton. CSIRO formed a research partnership with Monsanto for the Monsanto insect-proofing genes, and subsequently the herbicide tolerance genes to be included into the germplasm development program. The Monsanto-CSIRO research contract was backed by a Monsanto-CSD commercial contract. Monsanto, CSD, and CSIRO all receive royalties from the sale of the transgenic cotton seed and from the sale of licences that growers purchase to be able to grow the transgenic seed. CSIRO has been able to include mandatory management procedures in the license–this has been of seminal importance in preventing the buildup of resistance in the pest insect.

It soon became apparent that the Australian germplasm was among the best in the world, and in trials it proved to be successful in the United States and southern Europe. Cotton Seed Distributors then formed a wholly owned subsidiary company, Cotton Seed International (CSI), and CSIRO granted CSI sub-licensing rights from CSD to CSI for the CSIRO varieties to be sold internationally.

CSI formed a joint venture with Bayer (BCSI), and BCSI developed a cotton seed business in the United States, southern Europe and now in Brazil, with the parent Bayer agricultural company providing the distribution and seed sales activities. So, once again, the partnership extended along the business system and has proved to be successful, largely as a consequence of the excellence of the germplasm

and the quality of the lint.

Partnerships are successful when each partner has something to put in and receives appropriate recompense. The overall partnership between a public research institution, an Australian company, and a major multinational company has been successful. This is clearly an effective formula.

A Research Alliance

I want to introduce one other aspect of the partnership. Alongside the commercial partnership is a research alliance between Bayer and CSIRO. Both parties invest in a jointly agreed research program that is aimed at generating strong intellectual property positions. Some of these research projects are directed toward the cotton system, but not all. One output is a gene silencing methodology that is able to down-modulate any specified gene, and also can protect plants from viral infection. This discovery is subject to patent protection and is likely to have wide application.

In another industry in Australia, the wheat industry, we have a partnership, Graingene, which was formed to provide a critical mass of focused research directed at providing new traits in Australian wheat. We judged this to be necessary if Australia was to remain competitive in global trade. The unincorporated joint venture encompasses breeding of conventional and genetically modified varieties. The program is looking to the longer term as well as to the immediate future. CSIRO is in partnership with the Grains R&D Corporation, the principal funding agency for the wheat research industry in Australia, with the Australian Wheat Board, the international marketer for all of our wheat, and with the multinational company, Syngenta. Other research groups can be brought into the partnership when their skills are needed. Again, the partnership extends from the discovery phase to the delivery phase of research. The cultivars produced from the program are expected to be of high value to the Australian industry. This is proving to be the case. The Graingene program is illustrated in Figure 11.1.

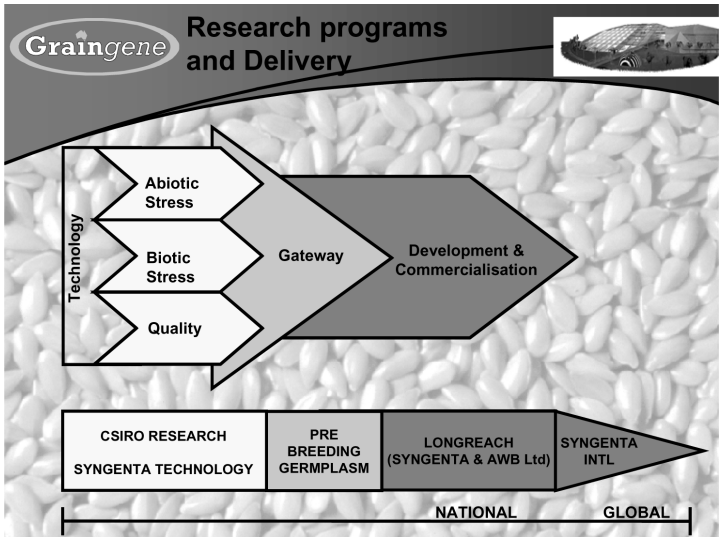


Figure 11.1. The "Graingene" program: discovery to delivery

The program has three major areas of research: abiotic stress, biotic stress, and grain quality. There is a technology program that provides new techniques and diagnostics to the breeder. Researchers work with germplasm chosen to be of value to the actual plant breeding program. We have a Gateway program that incorporates discoveries into suitable germplasm, which is then provided to breeding companies for development and subsequent commercialization. The first option to the improved material is to a breeding company, Longreach, which is owned by two of the partners of Graingene. The expectation is that they will develop most of the outputs from the Graingene program. We also anticipate that Syngenta will be able to take some of the outputs into international agriculture.

This partnership has similar properties to the successful cotton alliance, and already is proving successful in commercial outcomes and in the provision of support for longer term fundamental research, as well as for research more directed to the development of cultivars. A Graingene variety, based on carbon isotope discrimination, is proving to be remarkably successful, providing a major increase in yield in trials in the wheat belt of eastern Australia. A 20% increase in yield is a good indicator of the value of the partnership.

A rather different partnership is AUSGRAINZ where CSIRO Plant Industry and New Zealand Crop and Food recognized that they had complementary skills and infrastructure in plant biotechnology and plant breeding. This simple alliance has given rise to a number of commercially directed business systems. One of them is HRZ Wheats Pty Ltd, which is developing wheats for the high rainfall zone of Australia. The first varieties should hit the markets in 2006.

Conclusions

I have mentioned a range of partnerships and, in some of the cases, I have shown that these have given rise to further, derived partnerships, all tailored to fit modern biology and modern agribusiness. The development and introduction of an improved variety into actual agricultural systems is a complex process. It is quite apparent why partnerships are so essential (Figure 11.2).

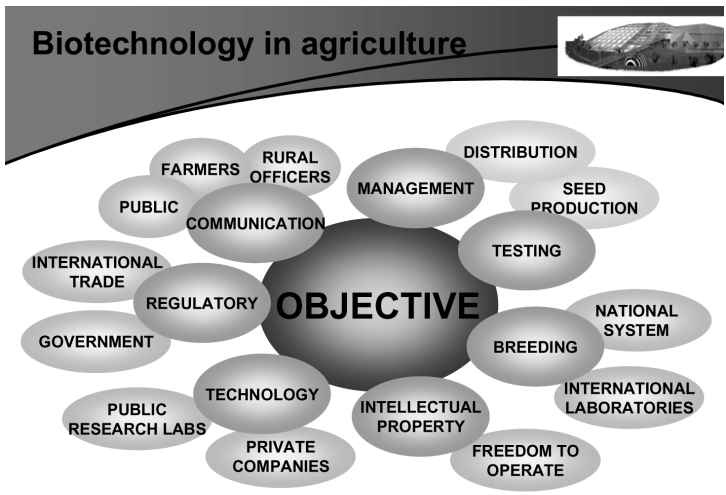


Figure 11.2. Partnerships to achieve objectives in agribusiness.

In the developing country perspective, the most important thing, I believe, is to define the key objective of the program. Rather than have general plans to improve all the agriculture of a region, I believe it is necessary to define the major opportunity or major problem, and then construct a partnership program involving partners from the developing country and from more sophisticated laboratories, all focused on achieving a common objective. Unfortunately, many externally funded development programs have failed because they lacked this focus on a desired outcome.

Partnerships structured around a common high-priority objective can be readily assessed at all stages, and adjustments can be made. I believe it is the way in which the more privileged countries can effectively help the rural poor of developing countries with the provision of food, with increasing the quality of life, and assisting a move toward economic self-sufficiency.

Chapter 12

Is Biosafety Only A First Step Toward More Sustainable Cropping Systems?

Brian R. Johnson and Anna Hope

Introduction

The impacts of new crops, new varieties of established crops, and the management systems needed to grow them have been a much-neglected area of research worldwide. In many cases novel cropping systems have been remarkably successful in agronomic terms, producing higher yields and enhanced resistance to pests and disease. The incorporation of high-yielding dwarf cereals to Asia is perhaps the best example of short-term gains, but iterative improvement in the agronomy of crops throughout the world has enabled agriculture to meet the needs of an increasing human population. In most cases new agricultural systems have been introduced without any consideration of environmental or socioeconomic impacts: these became apparent many years later with agriculturally induced soil degradation, rural unemployment, failing water resources, and pollution of air and water emerging as major global issues in the past 30 years.

Much of the agronomic success of new cropping systems has been derived from the use of agrochemicals and novel crop varieties with traits that enable farmers to increase yields to unprecedented levels. New methods of plant breeding, including transgenic technologies, have enabled the introduction of traits such as herbicide tolerance and insect resistance that enhance the efficiency and convenience of growing high-yield crops. As these new methods carry theoretical risks to humans and the environment, the use of crop plants derived from some forms of plant breeding, notably transgenic technology, have been subject to strict regulation that demands a risk assessment be undertaken prior to release. Such risk assessments have focused on impacts on human health and human and livestock nutrition, with some assessment of potential environmental impacts such as invasion, gene flow via cross-fertilization with wild relatives and other crop varieties, and toxicity to nontarget species.

Despite the efforts to assess biosafety of transgenic crops, in Europe and parts of Africa these crops and the food from them are still not widely accepted by regulators and the public, partly because perceptions of biosafety differ worldwide. Risk assessments performed in one market territory have often contained insufficient information to satisfy regulators elsewhere. It could be argued that biosafety assessments carried out in the US are too narrow in their scope for European regulators to be able to use them.

Case Histories of Risk Assessment–Too Little Too Late?

Bt maize

Consent for release of several Bt maize transformations was given by regulators in the US and Europe in the mid 1990s. Although it was recognized that some transformants contained high levels of the *Cry1Ab* toxin in the pollen grains, no evidence for impacts on nontarget species in the field was published and peer reviewed until 1999, when researchers from Cornell University demonstrated a possible impact of Bt pollen on Monarch butterflies (Losey *et al.*, 1999). The timing of such research was surprising as impacts on nontarget species were entirely predictable and frequently raised as an issue by ecologists throughout the 1980s and early 1990s (Tiedje *et al.*, 1989; Kareiva and Parker, 1994; Mellon and Rissler, 1995; Rissler and Mellon, 1996). Publication of reports of adverse impacts on Monarchs and other arthropods, even though they subsequently proved to be relatively unimportant to populations of nontarget insects (Sears *et al.*, 2001), caused considerable public and political disquiet, exacerbating the loss of market confidence in Europe. The media saw this episode both as an example of how transgenic crops could impact on the environment, and also as highlighting deficiencies in a risk assessment process that had failed to address potential impacts on nontarget species from an evidence base.

Herbicide-tolerant oilseed rape, maize, and beet

Herbicide-tolerant (HT) crops were developed in the US in the early 1990s, primarily to aid soil conservation and to make weed control easier and more cost effective. In the United States there was no assessment of the impacts of increased herbicide efficacy on nontarget plants and their associated food webs, partly because farmland-dependent biodiversity appears not to be an important issue in farmed landscapes in the US, where large areas of nonfarmed wilderness support extensive and rich ecosystems. In Europe, however, agriculture has been practiced over thousands of years; and farmland biodiversity is an integral part of the fabric of a landscape

dominated by agricultural use. Due to the production-driven rapid intensification of agricultural practices during the past 60 years, there is great concern about declining populations of noncrop plants, insects, and birds that inhabit farmland.

Research in the 1980s and 1990s had shown that this decline was partly due to increased use and efficiency of herbicides (Potts, 1986; Stoate, 1995), which had increasingly removed the noncrop primary biomass that supported higher trophic levels such as insects and birds. Early research by Read and Bush (1998) and Read and Ball (1999a, b) had shown that the use of HT transgenic crops could substantially increase the efficiency and reliability of weed control in beet, oilseed rape (canola), and forage maize. The UK statutory conservation agencies, led by English Nature, raised concerns in 1999 that the use of these crops would accelerate declines in farmland biodiversity, potentially reversing attempts by government to increase populations of farmland birds–a UK government policy target.

Glufosinate-ammonium-tolerant maize had already been given consent in the mid 1990s for commercial release in Europe, yet no consideration had been given to the potential indirect impacts on wildlife inherent in the mode of action of the transformation. Applications for commercial release of glufosinate-tolerant oilseed rape and glyphosate-tolerant sugar and fodder beet were also being assessed by EU regulators in the late 1990s. However, since the EU regulatory system contained no specific requirement to assess the "indirect" impacts of GM crops on biodiversity, it was not until 1999 that the UK regulatory system initiated further research, the so-called Farm Scale Evaluations (FSEs), aimed at evaluating the impacts on biodiversity of herbicides used with these crops, relative to conventional herbicide treatments. Results of these experiments (Firbank *et al.*, 2003) showed that the concerns expressed by the conservation organizations were supported in the case of GMHT spring-sown oilseed rape and beet.

These experiments marked the first time in the UK, and possibly in the world, that any novel cropping system had been evaluated for its impacts on biodiversity before introduction to commercial agriculture. This may seem surprising in the context of the introduction of other novel products and systems associated with medicine, machinery, consumer goods, and food into our environment. In these cases, risk assessment and potential environmental impact prior to introduction is routine, with rigorous monitoring usually carried out later to validate the assessments.

The failure of regulators to address indirect effects of the HT transformation on wildlife at an early stage in regulation led to heightened public concerns about the wisdom of adopting GM crops in general. This situation also led to widespread skepticism within the political system of the ability of regulators to properly evaluate the wider aspects of biosafety of transgenic crops. Reports were produced by UK parliamentary committees and commissions (for example Science and Technology Committee, 1999; AEBC, 2001), encouraging regulators to adequately address indirect impacts of GM crops. These reports were also concerned that the regulatory system had still not provided sufficient information on coexistence issues such as

gene flow between crops, and the control of volunteer GMHT crops that grow in fields from seed spilt at harvest.

The net result of the above situation was a 5-year delay in reaching a final decision about whether GMHT crops should be introduced into Europe on a commercial basis. The company developing GM glufosinate-tolerant maize, which ultimately received approval from the UK government, subsequently withdrew the crop from the market, arguing that the delay had rendered the variety no longer commercially viable, although the government experiments demonstrated that cultivation of this crop would be better for farmland wildlife than conventional maize growing.

Biosafety Issues Still Outstanding in Europe

For some transformations, especially those concerned with provision of tolerance to abiotic and biotic stresses, traits that could affect the fitness of either crops themselves or wild relatives that acquire transgene(s), there is still not enough information on impact. Most research has been concerned with mechanisms and rates of gene flow, but very few studies have investigated whether transgenes can increase components of fitness.

Snow and Jørgensen (1999) demonstrated that the glufosinate-tolerance trait is capable of introgressing into populations of canola (*Brassica rapa*) and persisting, even in the absence of favorable selection due to applications of this herbicide, but that gene transfer would not have adverse ecological consequences in environments where glufosinate is not used. More recently, Snow *et al.*, (2003) have shown that inheritance of a Bt gene encoding the insecticidal protein *Cry1Ac* from cultivated sunflowers into feral sunflowers *Helianthus annuus* led to decreased lepidopteran damage compared to control plants. Transgenic plants, constructed by backcrossing transgenic F1 hybrids into the wild parental background, produced up to 55% more seed than control plants in field trials. This demonstrated how a specific transgene can influence fecundity of a weedy plant, potentially increasing fitness, if fecundity is a key fitness component in this species, which is by no means certain.

Transgenic virus-resistant squash can be produced by inserting coat protein (CP) encoding sequences from plant viruses into the host genome (Quemada and Strehlow, 2002). Gene flow between cultivars and wild squashes can occur at low levels (Spencer and Snow, 2000), so virus resistance transgenes might be expected to transfer readily from transgenic squashes to wild plants. In this case, because the wild plants are so resistant to viruses (Provvidenti *et al.*, 1978), we might expect there to be little if any impact on fitness, with little introgression of transgenes into wild populations unless gene flow is very much higher than that found by Spencer and Snow. However, a study of the impact on fitness of F2 hybrids (Spencer and Snow, 2000) found a small increase in fecundity associated with virus resistance transgene introgression. Further research is clearly needed to resolve the question of

the impact of transfer of virus resistance transgenes in this group of plants.

Unsurprisingly, the net result of research so far on the impact of transgenes on ecological fitness has shown that it is likely to vary greatly depending on the transgene, the recipient organism, and the relationships between the organism and the environments that it inhabits in the wild. Assessment of risks associated with changes in fitness is likely to be a major challenge for researchers and regulators, if they are to satisfy risk-averse regulatory systems, environmental NGOs, and consumers.

Although there has been substantial research into toxicity of inbuilt pesticides to nontarget species, in Europe most of this has been in laboratory studies. As the Monarch butterfly research in the US demonstrates (Losey *et al.*, 1999; Sears *et al.*, 2001), such studies give little if any insight into what might happen in the field. In Europe there is still not enough evidence to convince politicians or the public that GM insect-resistant crops are generally safe for biodiversity, although some research relevant to European conditions has been initiated.

These issues of gene flow and impacts on fitness are relevant to the central issue of coexistence of transgenic plants with conventional and organic crops and with semi-natural ecosystems, identified as a key issue delaying the commercialization of transgenic crops in Europe.

Outstanding Regulatory Issues Worldwide

Crops do not usually invade natural ecosystems largely because they carry a substantial proportion of genes that give low fitness in the wild (Ellstrand and Hoffman, 1990), but some transformations aimed at countering abiotic stresses in arid areas could give crops or wild relatives greater fitness in certain habitats. Salt and drought tolerance are transgenic traits being actively studied in potentially invasive crops such as rice and grasses, to enable these crops to be grown in arid soils that are prone to salinity build-up, and even to be cultivated in estuarine situations. The ecosystems that have the greatest proportion of bare earth worldwide are deserts and estuaries, areas that are potentially prone to invasion by plants that are tolerant to drought and salinity. Given the fragility of these ecosystems and the importance of their wildlife, there is an urgent need for research to be commissioned now into whether salt-tolerant and drought-tolerant plants (crops and wild relatives, such as wild rice and natural grasses) have enhanced fitness in deserts and estuaries.

Herbicide-Tolerant Rice

The use of herbicide tolerance traits in rice could also have undesirable indirect impacts, not only on the environment but also on socioeconomic conditions in

developing countries. Herbicide-tolerant traits in rice are aimed at providing an alternative method of weed control to the traditional wetland cultivation used for centuries, enabling herbicide-tolerant rice to be grown on unirrigated land. This could increase yields, free up much-needed water resources for urban use, and reduce the amount of labor needed to produce rice, thereby potentially increasing profits. However, wetland rice areas hold a substantial proportion of global wetland wildlife, with many populations of birds and amphibians now almost entirely dependent on flooded rice fields for wintering and breeding habitat (BirdLife International, 2001). Conversion to dryland cultivation would have an adverse impact on these populations on a global scale. Dryland cultivation might well be more profitable due to reductions in labor, but in developing countries this could mean greater rural unemployment with disruption of the socioeconomic fabric in the countryside, increased migration to urban areas, and loss of skills in wetland rice production.

Assessing Sustainability of Novel Cropping Systems

The introduction of a novel cropping system, however it is derived, can have a very wide-ranging impact on the environment and on the socioeconomic fabric of rural areas. Novel cropping systems can also have impacts on soil structure and function–a serious issue in developing countries–carbon balance and water resources. These impacts cannot all be considered within the present framework of biosafety regulation, and nontransgenic crops are largely unregulated, yet they should be considered by those who have to decide whether to permit and/or promote the introduction of the increasingly wide range of cropping systems being developed worldwide.

Clearly assessment of the biosafety of food plants and the systems by which they are grown is of paramount importance so far as human and livestock safety are concerned, and risk assessment must be the first hurdle that a novel crop should pass before it is used in food production. But there are much wider considerations that are equally important to assess when a novel crop or variety will lead to changes in agricultural systems, and these should be formalized into a second hurdle to be addressed by decision-makers. Given the environmental damage and unsustainable finite resource consumption currently inherent in high productivity agriculture, these wider issues should be considered in the context of relative sustainability assessments, comparing the overall sustainability of novel cropping systems with their “conventional” counterparts, wherever possible using comparative scientific methodology such as that used in the design of the UK farm-scale evaluations. Objective comparisons of socioeconomic impacts should also form part of sustainability assessments, together with consideration of net carbon balance impacts and use of finite resources such as water, fossil fuels, and phosphates.

To apply these principles to transgenic crops alone is unreasonable and cannot be defended scientifically. Novel crops and the systems under which they are grown can arise from almost any form of plant breeding, together with development of agrochemicals that aid their cultivation and growth. Genomic 'mining' coupled with marker-assisted breeding is almost certain to produce crops with traits similar to transgenics, with similar implications for risks to humans and the environment, and similar impacts on agricultural sustainability, some positive and some negative. We need a global framework to compare biosafety and relative sustainability of these systems, derived from the lessons learnt from the introduction of GM crops, but applied to all novel cropping systems. This may seem at first sight to be a potentially onerous task, but as the field-scale evaluations have shown, methodologies could be developed to enable such comparisons to be done quickly and efficiently.

Conclusion

The regulation and development of transgenic crops has shown that not only is there a need to develop productive and more sustainable cropping systems, but there is also the need to demonstrate with sound scientific evidence that they really are more sustainable. Without such evidence public and political acceptance of new ways of producing food is likely to be fraught with difficulty and delay. Risk assessment alone is but the first step in the process of assessing whether a crop is safe to use in a specific environment. However, assessment of the overall sustainability of a novel cropping system in relation to existing systems is as important as biosafety in the narrow regulatory sense. Given the scale of the impact of agriculture on the global environment, the question "is this crop safe to eat and environmentally safe?" is too narrow in scope to address the wider question: "Yes it is safe, but would its use be more sustainable than what we have now?" This question is increasingly occupying the minds of strategic planners of world agriculture. Such a question deserves to be addressed by scientific enquiry to produce the evidence needed to inform crucial decisions about changing agricultural systems, whatever their origin.

References

AEBC. 2001. (Agriculture and Environment Biotechnology Commission) Crops on Trial. http://www.aebc.gov.uk/aebc/pdf/crops.pdf.

BirdLife International. 2001. Saving the Rice Fields, Saving the Birds. BirdLife International, Brussels.

Ellstrand, N.C., and C.A. Hoffman. 1990. Hybridization as an avenue of escape for engineered genes: Strategies for risk reduction. BioScience 40(6): 438-441.

Fowle III, John R. 1987. Application of Biotechnology: Environmental and Policy Issues. Westview Press, Boulder, Colorado, USA.

Firbank L.G., J.N. Perry, G.R. Squire, D.A. Bohan, D.R. Brooks, G.T. Champion, S.J. Clark, R.E. Daniels, A.M. Dewar, A.J. Haughton, C. Hawes, M.S. Heard, M.O. Hill, M.J. May, J.L. Osborne, P. Rothery, D.B. Roy, R.J. Scott, and I.P. Woiwod. 2003. The implications of spring-sown genetically modified herbicide-tolerant crops for farmland biodiversity: A commentary on the Farm Scale Evaluations of Spring Sown Crops. http://www.defra.gov.uk/environment/gm/fse/results/fse-summary.pdf.

Halvorson, H.O., D. Pramer, and M. Rogul. 1985. Engineered Organisms in the Environment: Scientific Issues. American Society for Microbiology, Washington, D.C., USA.

Kareiva, P., and I. Parker. 1994. Environmental Risks of Genetically Engineered Organisms and Key Regulatory Issues. Greenpeace International.

Losey, J.O, L. Rainier, and M. Carter. 1999. Transgenic pollen harms monarch larvae. Nature 399:214.

Mellon, M., and J. Rissler. 1995. Transgenic crops: USDA data on small-scale tests contribute little to commercial risk assessment. Bio/Technology, 13: 96.

Provvidenti, R., R.W. Robinson, and H.M. Munger. 1978. Multiple Virus Resistance in Cucurbita species. Cucurbit Genetics Cooperative Report 1:26-27 New York Agricultural Experiment Station, Geneva NY 14456.

Read, M.A., and M.N. Bush. 1998. Control of weeds in genetically modified sugar beet with glufosinate-ammonium in the UK. Aspects of Applied Biology 52: 401-406.

Read, M.A., and J.G. Ball. 1999a. Control of weeds in genetically modified crops of winter and spring oilseed rape with glufosinate-ammonium in the UK. Aspects of Applied Biology 55: 27-33.

Read, M.A., and J.G. Ball. 1999b. The control of weeds with glufosinate-ammonium in genetically modified crops of forage maize in the UK. Proceedings of the British Crop Protection Conference–1999–Weeds, 847-852.

Rogers, M. 1977. Biohazard. Alfred Knopf, New York.

Levin, M., and H. Strauss. 1991. Risk Assessment in Genetic Engineering: Environmental Release of Organisms. McGraw Hill, New York.

Potts, G.R. 1986. The Partridge. Pesticides, Predation and Conservation. Collins, London.

Rissler, J., and M. Mellon. 1996. The Ecological Risks of Engineered Crops. Cambridge, MA: The MIT Press. xii + 168 pp.

Science and Technology Committee. 1999. Scientific Advisory System: Genetically Modified Foods. Report No.1; Session 1998/1999 http://www.publications.parliament.uk/pa/cm199899/cmselect/cmsctech/286/28604.htm.

Sears, M.K., R.L. Hellmich, D.E. Stanley-Horn, K.S. Oberhauser, J.M. Pleasants, H.R Mattila,., B.D. Siegfried, and G.P. Dively. 2001. Impact of Bt corn pollen on monarch butterfly populations: a risk assessment. Proceedings of the National Academy of Sciences USA 98: 11937-11942.

Snow, A.A., and R.B. Jørgensen. 1999. Fitness costs associated with transgenic glufosinate tolerance introgressed from Brassica napus ssp oleifera (oilseed rape) into weedy Brassica rapa. In Gene Flow and Agriculture: Relevance for Transgenic Crops. BCPC Symposium Proceedings No. 72, 137-142.

Snow, A.A., K.L. Uthus, and T.M. Culley. 2001. Fitness of Hybrids Between Weedy and Cultivated Radish: Implications. Ecological Applications. 11 (3): 934-943.

Snow, A.A., D. Pilson, L.H. Rieseberg, M.J. Paulsen, N. Pleskac, M.R. Reagon, D.E. Wolf, and S.M. Selbo. 2003. A Bt transgene reduces herbivory and enhances fecundity in wild sunflowers. Ecological Applications 13:279-286.

Spencer, L.J., and A.A. Snow. 2000. Vigorous hybrids? A comparison of fitness among wild gourds and three generations of transgenic wild-crop hybrid squash (Cucurbita pepo). 40th Annual Meeting of the Weed Science Society of America, Toronto, Ontario, Canada, February 7, 2000.

Stoate, C. 1995. The changing face of farming and wildlife. Part 2: 1945-1995. British Wildlife 7: 162-172.

Tiedje, J.M., R.K. Colwell, Y.L. Grossman, R.E. Hodson, R.E. Lenski, R.N Mack, and P.J. Regal. 1989. The planned introduction of genetically engineered organisms: Ecological considerations and recommendations. Ecology 70: 298-315.

Wright, Susan. 1990. Preventing a Biological Arms Race. The MIT Press, Cambridge, Massachusetts.

Chapter 13

Precautionary Regulation Prevents Use of Green Biotechnology in Public Projects

Ingo Potrykus

Introduction

In developing countries, over 500,000 people become blind each year, and up to 6000 die every day from vitamin A malnutrition. This tragedy continues despite enormous efforts from public and philanthropic institutions to reduce these problems with the help of traditional interventions such as supplementation, fortification, and encouragement to diversify diets. This heavy toll poor people in developing countries are paying will continue if we do not find a way to complement traditional interventions by sustainable and unconventional ones. One of those could be based on nutritional improvement of basic staple crops through "biofortification"–genetic improvement of micronutrients and vitamins. Plant breeding and genetic engineering offer two complementary approaches.

The major deficient micronutrients are iron, zinc, and vitamin A. Vitamin A deficiency is widespread amongst the rice-dependent poor, because rice does not contain any pro-vitamin A. (Plants do not produce vitamin A itself, but pro-vitamin A (carotenoids), which our body converts into vitamin A.) Dependence on rice therefore leads to vitamin A deficiency if poverty prevents a diversified diet, and affects children and pregnant women most severely. The medical consequences for the 400 million rice-consuming poor are severe: impaired vision (in extreme cases irreversible blindness), impaired epithelial integrity against infections, reduced immune response, heamopoieses, and poor skeletal growth. Rice containing pro-vitamin A could substantially reduce the problem, but "biofortification" of rice for pro-vitamin A is not possible without genetic engineering. The transgenic concept, therefore, was based on the idea of introducing all genes necessary to activate the biochemical pathway leading to synthesis and accumulation of pro-vitamin A in the endosperm (the starch storage tissue of the seed).

Scientific Breakthrough in Rice with Pro-Vitamin A

"Golden Rice" contains the genes necessary to activate the biochemical pathway for pro-vitamin A. This pathway is activated exclusively in the endosperm. The intensity of the "golden color" represents the concentration of pro-vitamin A. There are different lines with different concentrations. We aim at concentrations where a daily diet of 200 g of rice will provide enough pro-vitamin A to substantially reduce vitamin A deficiency. The concentration required for this purpose could only be determined when data from bioavailability studies are available. Experiments are in progress and will continue until late 2005. So far we are working with lines in which, theoretically, the concentration is high enough for our goal.

The novel trait has been transferred into several Indica rice varieties–especially IR64, the most popular rice variety of Southeast Asia, and "regulatory clean" events have been selected to facilitate the processing through the deregulatory process.

Delivery of "Golden Rice"

Golden Rice will be made available to developing countries in the framework of a "Humanitarian Golden Rice Project." This was, from the beginning, a public research project designed to reduce malnutrition in developing countries. Thanks to strong support from the private sector and donations of "free licences for humanitarian use" for intellectual property rights involved in the basic technology, the hurdle of extended IPR linked to the technology used in the scientific project could be overcome. This enables us to collaborate with public rice research institutions in developing countries based on "freedom-to-operate" toward the development of locally adapted Golden Rice varieties.

Once Golden Rice varieties have passed the national biosafety procedures, they will be made available to subsistence farmers free of charge and without limitations. It will become their property, and they can–year after year–use part of their harvest for the next sowing. The farmers will use their traditional farming systems and they will not require any additional agronomic inputs. Therefore, there will be no "new dependencies." There is no conceivable risk to the environment that would justify not growing Golden Rice in the field for breeding and up-scaling reasons.

This progress, since the scientific breakthrough in 1999, was made possible through a novel type of public-private partnership. Thanks to an agreement with Syngenta and other agbiotech industries, the use of Golden Rice is free of licenses for "humanitarian use," defined as "income from Golden Rice per year and farmer below US$10,000." "Commercial use," however, (above US$10,000 per year) requires a license from Syngenta. Humanitarian use is based on (license-free) sublicenses from the Humanitarian Golden Rice Board (contact: Professor Ingo Potrykus) to public rice research institutions. This sublicense agreement ensures that

the material is handled according to established genetically modified organism (GMO) rules and regulations, and that the target population–subsistence farmer and urban poor–receive the material without any additional cost for the trait.

Locally adapted rice varieties being developed

Development of locally adapted Golden Rice varieties as well as application to national bioregulatory authorities for field testing and deregulation is in the hands of national and international public rice research institutions. To date this "Humanitarian Golden Rice Network" includes 16 institutions in Bangladesh, China, India, Indonesia, South Africa, The Philippines, and Vietnam. The network is under the strategic guidance of the Humanitarian Golden Rice Board, and under the management of a network coordinator with offices at the International Rice Research Institute (IRRI), Philippines.

Delivering Biofortified Seeds for Micronutrient Deficiencies

Biofortification (complementation for missing micronutrients with the help of genetic complementation) of the basic staple crops for poor populations in developing countries is, most probably, the most sustainable and cost-effective approach to reduce micronutrient malnutrition. (For more information on the concept of bio-fortification and a recent challenge program of the CGIAR see homepage www.harvestplus.org.) Golden Rice represents the first example of biofortification achieved via genetic engineering. Research investment for this trait (biofortification for pro-vitamin A) was relatively modest (US$2.4 million over nine years), and financed from funds for basic research and the support of the Rockefeller Foundation.

Product development, however, from this scientific breakthrough is time-consuming and requires additional funding, but again one-time only for each event. Expenses are increasing dramatically when working through the biosafety assessments required for deregulation. Again this is a one-time investment. As soon as a novel biofortified variety is deregulated and can be handed out to the farmer, the system demonstrates its unique potential, because from this point on, the technology is built into each and every seed and does not require any additional investment for an unlimited period of time. Just consider the potential of a single Golden Rice seed: Put into soil it will grow to a plant that produces, at least, 1000 seeds; a repetition will yield at least 1 million seeds; the next generation produces 1 billion seeds and so on. These represent 20,000 tonnes of rice, and it takes only two years to produce them. From these 20,000 tonnes of rice 100,000 poor people can survive for one year. If they use Golden Rice, they have an automatic vitamin A supplement, and this

protection is cost-free and sustainable. All a farmer needs to benefit from the technology is one seed. There is no additional input required over "normal" rice. For urban poor there is no premium on vitamin A-rice. There are enough seeds to be handed out to many farmers, but this cannot be done because Golden Rice is a GMO and those are highly regulated. The Humanitarian Golden Rice Board has decided to follow the established rules and regulations.

Timelines for product development

It took 10 years (from 1980 to 1990) to develop the necessary technology to place genes into rice. It took a further 9 years (from 1990 to 1999) to introduce the genes required to establish the biochemical pathway leading to pro-vitamin A in the seed. It took a further 5 years (from 1999 to 2004) to develop a Golden Rice "product" and carry it across a series of GMO-specific hurdles such as intellectual property rights (IPRs). In addition, it will take, probably, at least 5 more years to advance the first Golden Rice product through the deregulatory procedures. Therefore, it will take about 30 years if we include technology development. Considering that Golden Rice could substantially reduce blindness (500,000 per year), and death (2-3 million per year) 30 years is a very long time period, and certainly not "too fast." If it were possible to shorten the time from discovery to the deregulated product, we could prevent blindness for hundreds of thousands of children.

Risk Assessment Procedures for Golden Rice

The next five years will have to be spent on the required "biosafety assessments" to guarantee that there is no putative harm from Golden Rice, for the environment and the consumer. Nothing speaks against a cautious approach, but present regulatory practices follow an extreme interpretation of the "precautionary principle," with the understanding that not even the slightest hypothetical risks can be accepted or left untested, and at the same time all putative benefits are totally ignored.

Golden Rice and the problem of environmental risk assessment reveal the difficulty of the present system. The biology of the golden rice system–low amounts of additional b-carotene in the endosperm in plants that are loaded with b-carotene in every organ except the root–does not provide for any selective advantage in any environment, and therefore cannot pose any substantial risk. Despite this fact, Golden Rice is still awaiting permission for the first small-scale field release, in which environmental risks have to be studied experimentally. Golden Rice could prevent blindness and death of hundreds of thousands of children, but must await a protracted risk assessment, ignoring a risk-benefit analysis.

Cost of regulatory procedures

What then is required for the deregulatory procedure? First, it is advisable to focus on one carefully selected transgenic event, which is as "regulatory clean" as possible. It must not include characters that are a priori unpopular with regulatory authorities, such as "multiple integrations," "rearrangements," "read-through across T-DNA borders," "microbial origins of replication," or "ballast DNA." This requires the production of hundreds of similar transgenic events with the same DNA construct. This construct itself must have been assembled taking into account the requirements of the regulatory authorities in the later deregulation process. Only when working on the basis of a "regulatory clean construct" and with "regulatory clean transformation technology" is there a chance to survive the deregulation. Such a carefully selected event can then be used to start the series of biosafety assessment experiments traditionally expected to prove or disprove any putative biosafety hazard. The consequence of this approach is that nearly 99% of transgenic events, and often those with the highest levels of expression, have to be discarded. Already this first step of mass production of many hundreds of similar events and subsequent destruction of most is beyond the scope of any public research institution, not only in developing but also in industrial countries. No funding agency would be willing to finance this step. This is, however, the first prerequisite for entering the deregulation procedure with some chance for success.

Once the right material is ready, biosafety assessment can start. There are "event-independent" studies that refer to the introduced genes and their function in general, and which are valid for all events produced with these genes. "Exposure evaluation" (for the novel trait, for example, pro-vitamin A in rice) studies the intended use and bio-availability. This study alone takes about three years, because the material has to be produced in specific plant growth chambers, due to the lack of permission for field release. "Protein production and equivalence" analyzes the proteins through which the genes fulfil their function. For this purpose the proteins have to be isolated from the plant, biochemically characterized, and their function confirmed. Lack of homology to toxins and allergens, rapid degradation in gastric/intestinal studies, heat lability, acute toxicity in rodent feeding, screening for further putative allergens and toxins are assumed to ensure that no unintended toxin or allergen will be consumed with Golden Rice. Most people have eaten these genes and gene-products throughout their life from other food sources.

There are also "event-dependent" studies required:

- "Molecular characterization and genetic stability," including: single copy effect; marker gene at same locus; simple integration; Mendelian inheritance over at least three generations; no potential gene disruption; no unknown open reading frames; no DNA transfer beyond borders; no antibiotic resistance gene or origin of replication; insert limited to the minimum necessary; insert plus flanking regions sequenced; phenotypic evidence and biochemical evidence for stability over three generations.

- "Expression profiling" involving gene expression levels at key growth stages; evidence for seed-specific expression.
- "Phenotype analysis" involving field performance, typical agronomic traits, yield compared to isogenic lines; pest and disease status same as origin.
- "Compositional analysis" involving data from two seasons times six locations times three replications on proximates, macronutrients and micronutrients, antinutrients, toxins, allergens; data generated on modified and isogenic background.
- "Environmental risk assessment" that requires 4-5 years of an entire research team.

Cost of regulatory procedures

No scientist or scientific institution in the public domain has the potential, funding, or motivation to perform such biosafety experiments. It is, therefore, no surprise that virtually all transgenic events taken through the deregulatory procedure are (directly or indirectly) from the private sector, and carry the potential for substantial financial reward. Humanitarian projects to benefit the poor obviously do not fall into this category, although the benefit would apply to many millions. There is a lot of support in the public sector worldwide to exploit green biotechnology for the benefit of the poor in developing countries. If our society continues with the present "extreme precautionary" approach to biosafety assessment, it is absolutely unrealistic to invest any further funds in public research for this purpose. Of course, there would be interesting scientific progress, but no products, and especially no products passing through regulation. Consequently, all this work will have no practical output and the target population would not benefit.

Why then do we have this GMO regulation? Firstly, there are historic reasons. At the beginning of GMO technology development it was sensible to be careful ("precautionary"). The scientists at that time, working not with plants but with human-pathogenic microorganisms, established regulations based on the notion that the consequence of the technology could lead to "unpredictable genome alterations." Experience after 20 years working with transgenic plants and their practical application on 50 million hectares of farmland, as well as from many hundreds of "biosafety" experiments in which biosafety questions in the context of transgenic plants have been carefully studied, led to numerous original publications and reports from academic institutions that all came to the same conclusion. There is no specific risk associated with the technology that would exceed risks inherent in traditional plant breeding or natural evolution. (For a discussion on the moral imperative of the use of genetically modified crops in developing countries, see Nuffield Council on Bioethics, discussion paper January 2004, homepage www.nuffieldbioethics.org.)

Why then do we maintain GMO regulation and even extend it to ever more extreme precautionary regulation? The answer to this question often follows the

notion that we have to do so to build trust in the technology for its acceptance by the consumer. Experience with this strategy over the last 10 years, however, demonstrates clearly that this approach did not work in Europe and many developing countries, and this is not surprising. How could citizens understand that their government is regulating a technology in an extremely restrictive manner, if this technology is without specific risks? Unbiased citizens will, of course, assume that their government is taking rational decisions, and the technology must be as dangerous as the regulation implies.

Consequently, maintenance of extreme precautionary regulation builds mistrust instead of trust. Why then do we not at least clear regulation from all scientifically unjustified and opportunistic ballast to build a rational regulatory procedure? It seems that not many institutions have the interest or the political power to do so. If we consider the potential GMO technology has with regard to food security in developing countries, then numerous international organizations should have an interest, but neither FAO, WHO, nor UNIDO will have the courage and power to do so. What price is our society paying for this opportunistic attitude toward an established "extreme precautionary regulatory" system, functioning worldwide? The attitude seems to be that "GMO technology will not reduce hunger and malnutrition, and will not protect the environment in developing countries." The use of the technology will be restricted to "luxury projects," with safe financial returns to the private sector and in industrial countries. There will, of course, be some spin-offs from these projects into developing countries, and these may even carry some benefits for the poor, such as "insect-resistant cotton," but there will be no product development focusing on urgent and specific needs of the poor in developing countries, such as "food security."

Gene Technology and Plant Breeding

Gene technology has the potential to support and to complement traditional plant breeding. In the context of the discussion on GMO regulation, which is justified with the argument that genetic engineering leads to "unpredictable genome alterations," it may be helpful to remember a few basic facts concerning all our plant-based food that is derived from crop plant varieties. Without exception they have been developed through traditional plant breeding.

Plant breeding uses the technique of "crossing followed by selection," to combine traits of agronomic and nutritional interest and to exclude undesired traits. Starting materials for this procedure are "landraces" of crop plants, originally identified and selected by indigenous farmers. Landraces differ from each other in traits because they differ in "mutations." Mutations are "unpredictable genome alterations." In the course of traditional breeding the technology adds automatically (but not deliberately) (in parts very dramatic) "unpredictable genome alterations such as "recombinations," "translocations," "deletions," and "inversions." These

"unpredictable" and "most severe" genome alterations are accumulated at every breeding step and each new traditionally bred variety is thus based on, and characterized by, an increasing array of such genome alterations. With the progress of the breeding process, varieties are combined with varieties, often with related wild relatives of the crop plants, often further altered in their genome by induced mutations. All our modern crop varieties–from which we derive our food–have a long history, and are composed of numerous previous varieties. There is little doubt that all our traditionally bred crop varieties are extensively "genetically modified" by hundreds if not thousands of "unpredictable genome alterations."

This approach is exemplified in the breeding that led to IR64, the most popular Indica rice variety, developed at the International Rice Research Institute in the Philippines, and grown all over Southeast Asia. The original rice genome was "genetically modified" by "mutations," "recombinations," "translocations," and "deletions" to finally arrive at the genome of IR64. IR64 and any other varieties that have been channeled into the breeding tree have not been subjected to a "biosafety assessment." Billions of consumers in developing countries have consumed IR64 (as all the other rice or crop varieties) and survived on this and the earlier varieties without any harm, and there was no unpredictable harm to the environment. This holds true for all the other varieties in all other crops, despite all the "most dramatic and unpredictable alterations to the genome."

"Genetically engineered" varieties differ from the "genetically modified" ones in small, precise, similar, and well-studied alterations. For Golden Rice, we have taken variety IR64 and added two precisely defined genes into the 50,000-gene genome of rice, using a technology that is by orders of magnitude more precise than traditional breeding. This provided pro-vitamin A in the seed, which would reduce vitamin A malnutrition. This is an example of a "genetically engineered" variety, or a "GMO." The plant is now falling under "extreme precautionary" regulations, despite the fact that the engineering step is, in comparison to the history of IR64, extremely small, perfectly predictable, well studied, and without any greater risk to the consumer or the environment.

Our experience with traditionally developed crop varieties tells us very clearly that "unpredictable genome alterations" are not an argument for extreme regulation. Why are they now, and beyond any logic, the key argument for extreme regulation of "genetically engineered" plants? The argument that genes may come from different organisms and would never have found their way into a GMO cannot be accepted as well. Genes are connected by a continuum in evolution, and are closely related, and the "crossing barrier" between species is a mechanism to advance evolution within a species, but not to prevent introduction of genes. Why are GMOs singled out from the normal breeding tree and treated according to the established rules and regulations of an extreme precautionary principle, thus preventing their sensible use to the benefit of the poor?

Conclusion

What are the consequences of the extreme precautionary regulation of green biotechnology for public research toward food security in developing countries? There are numerous scientists and institutions in developing countries that have the capacity, motivation, and often even funding to work toward scientific progress in the areas of resistance to pests, diseases, drought, heat, cold, salinity, and heavy metal tolerance. There is the potential to rescue harvests and to expand agricultural productivity in hostile environments; to improve photosynthetic efficiency and to enhance the exploitation of natural resources to increase productivity; and to enhance nutritional content to reduce malnutrition with regard to micronutrients such as vitamin A. Very few of them, however, have the financial and mental capacity to transform a scientific success into an applicable "product," which is the first prerequisite for benefit of the poor from a scientific advance. Probably no scientist nor institution in the public domain, however, has the resources, experience, and determination to carry a single GMO product across the hurdles of today's extreme precautionary regulatory procedures. Regulatory authorities in developing countries are less experienced, more insecure, and more stringent than their colleagues in industrial countries. Even with support from the experienced private sector, deregulation of a novel GMO product has become a gigantic task. It is, therefore, obvious that if we continue with the present regulatory standards, the potential of green biotechnology will not reach the poor.

Let me close with a quote from the follow-up discussion paper of the Nuffield Council on Bioethics 2004: "We believe EU regulators have not paid enough attention to the impact of EU regulations on agriculture in developing countries."

Our societies have wasted too much time in a long phase of "risk-obsession." Putative benefits by far outrank the "phantom risks." It is time to return to common sense.

References

Beyer, P., S. Al-Babili, X. Ye, P. Lucca, P. Schaub, R. Welsch, and I. Potrykus. 2002. Golden Rice: introducing the b-carotene biosynthetic pathway into rice endosperm by genetic engineering to defeat vitamin A deficiency. J Nutrition 132: 506S-510S.

Tran Thi Cuc Hoa, Salim AlBabili, Patrick Schaub, Ingo Potrykus, and Peter Beyer. 2003. Golden Indica and Japonica rice lines amenable to deregulation. Plant Physiology 133: 161-169.

Ye, X., S. Al-Babili, A. Klöti, J. Zhang, P. Lucca, P. Beyer, and I. Potrykus. 2000. Engineering provitamin A (b-carotene) biosynthetic pathway into (carotenoid-free) rice endosperm. Science 287: 303-305

Chapter 14

Diversity Arrays Technology: A Novel Tool for Harnessing the Genetic Potential of Orphan Crops

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Introduction

Genetic diversity is the raw material available to plant breeders. By productively recombining genetic diversity, plant breeders have been successfully producing, year after year, improved cultivars of the major domesticated species used in the world's diverse agricultural systems. Molecular genetic markers offer a powerful tool to accelerate and refine this process. Existing genetic marker (genotyping) technologies, mostly developed for applications in human health, have also been applied successfully to agricultural species, but their cost remains prohibitive for most agricultural applications. This is particularly true for species for which no molecular data and very limited resources are available.

Because of the limitations of existing marker technologies, we have developed Diversity Arrays Technology (DArT), a novel method to discover and score genetic polymorphic markers. DArT is a sequence-independent, high-throughput method, able to discover hundreds of markers in a single experiment. DArT markers are typed in parallel, using high-throughput platforms, with a low cost per data point. With DArT, plant breeders, plant ecologists, as well as the managers of the germplasm collections, will be able to perform genetic analysis in a cost-effective and high-throughput manner. DArT fingerprints will be useful for accelerating plant breeding, and for the characterization and management of genetic diversity in domesticated species as well as in their wild relatives.

We have developed DArT successfully for rice, barley, wheat, and cassava. We have also produced a dedicated data management and analysis package, a key part of the technology, entirely built from Open Source components. Work is in progress to establish DArT for other species of importance to tropical agriculture: pigeonpea, sorghum, and chickpea. We have a strong interest in developing partnerships to establish DArT for many species, and we are developing a network model for the delivery of technology to users.

Whole Genome Profiling

The genetic diversity present within species is one of the components of biological systems. In many cases, a high level of diversity provides robustness to natural ecosystems and maximizes their opportunity for further diversification. Natural ecosystems are increasingly managed by humans with the objective of maintaining the existing genetic diversity. This diversity is considered an insurance against catastrophic damage and a resource for future human use. In agricultural ecosystems, management by the farmer is the key determinant of genetic diversity. It is well established that biological diversity contributes to the robustness and sustainability of agricultural production systems, particularly in developing countries where societal support to farmers in time of crisis is limited or nonexistent (Conway, 1999).

A well-known example of the danger of limited diversity within a cultivated species is the 1970 epidemic of southern leaf blight in the Corn Belt of the USA. The quasi-universal adoption in the 1960s of hybrid maize cultivars produced using T cytoplasmic male sterility led to the loss of about 15% of the US maize crop in the early 1970s, because the cultivars were susceptible to the new race T of *Helminthosporium maydis.* Although the economic loss was large for the commercial farmers involved, a similar event in a subsistence agricultural system would have had more devastating consequences.

Measuring genetic diversity for many species is not an easy task. Molecular genetic markers, based on DNA sequence polymorphism, are increasingly used to complement phenotypic and protein-based markers. Over the past 20 years, DNA-based markers have been established in many species, mostly agricultural crops. Molecular markers linked to desirable traits have been used to accelerate plant breeding (Ribaut and Hoisington, 1998), for example by replacing phenotypic assays with single-marker assays when possible and cost effective (Bonnett *et al.,* 2004). Many traits of interest to plant breeders, however, are complex and polygenic. Therefore the creation of an adapted elite variety will increasingly involve the deliberate combination of various genomic regions from many different individuals (Peleman and van der Voort, 2003). Comprehensive knowledge of genetic diversity in the cultivated and wild germplasm–the source of novel genomic regions, novel alleles, and novel traits (Xiao *et al.,* 1998; Li *et al.,* 2003)–is very important. Applying molecular markers in this context requires moving from single marker

assays to genome-wide marker profiles: genomic fingerprints covering genetic diversity at hundreds of loci. For genetic diversity analysis also, a reliable measure of the differences and the relatedness between individuals will require whole-genome profiling. We briefly review the marker systems suitable for whole-genome profiling. We then present our current work on the development of DArT, a novel marker system invented by one of us (A. Kilian), and particularly suitable for the analysis of genetic diversity in orphan crops and wild species (Jaccoud *et al.*, 2001).

Limitations of Existing Technologies

Current molecular marker technologies include RFLP, AFLP®, SSR (microsatellites), and SNP. All have at least one of the following limitations:

- The discovery of a sufficiently large number of polymorphic markers to achieve genome coverage is slow because it is a sequential process.
- Some marker systems are based on sequence information. For many plant species it may not be practical or economical to determine a large amount of genomic sequence, particularly if different alleles have to be identified by sequencing, for example when sources of new alleles are discovered.
- Once markers are identified, the cost of scoring the markers ("genotyping ") is high and the throughput low. For SSR and SNP markers an assay has to be developed first. This often results in only a fraction of the candidates identified being retained for routine use. Markers are then typically scored one by one (or at a modest level of multiplexing), usually using gel-based systems.

AFLP®, is a proprietary, cost-effective method to discover and type polymorphic DNA sequences. The main limitations to its use in its current format are:

- Scoring is done by electrophoresis on gels (limited throughput).
- An allele is represented by the size of a band on the gel, which can be difficult to assess objectively.
- Typing of new varieties of a species can be done under the hypothesis that bands of identical size represent the same allele of the same locus, which is not always true.
- Cloning the polymorphic bands is a labor-intensive and sequential procedure.

Simple Sequence Repeat markers (Microsatellites; SSR) also have limitations:

- The marker discovery phase is expensive and involves DNA sequencing. A standard team of two persons in a well-supported environment is able to develop approximately 100 reliable SSR markers per year. Although availability of genome or EST sequence data would accelerate the discovery process, the development of

a reliable subset of polymorphic SSR markers remains a laboratory-based empirical task.

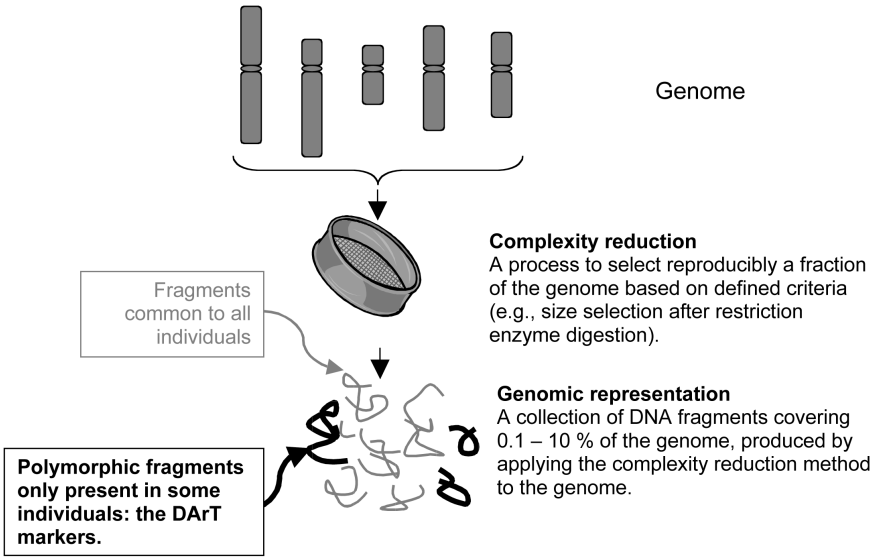
- A high-resolution gel equipment system is required for genotyping. This still is an expensive piece of equipment to purchase and service. The throughput is limited by the reliance on electrophoresis and gels.
- Marker scoring usually requires one amplification reaction per marker; therefore the analysis is sequential not parallel. After extensive development work, some markers can be multiplexed up to 10 markers per reaction in the best case, thereby reducing the number of reactions required. However, the cost of the assay development to achieve this level of multiplexing is such that it is unlikely to be performed for species other than humans and a few major crops.
- The cost of producing an SSR data point is about US$1, once the polymorphic SSR is discovered and the scoring protocol is well established. A genome-wide genotype of 500 established SSR markers for 100 plants would therefore cost about US$50,000.

Single Nucleotide Polymorphisms are the preferred markers in human genotyping. Their application to other species, however, is limited by two important factors:

- Although high-throughput methods are being developed for scoring of SNP markers, most methods still require a marker-specific amplification reaction, or marker-specific primers, oligonucleotides, or probes.
- Although the cost per data point for well-formatted SNP markers is expected to decrease to approximately US$0.20, the initial investment required for marker discovery (sequencing of allelic variants) and assay development remains prohibitive for many agricultural species, at least for the foreseeable future.

Diversity Arrays Technology

DArT was developed to provide a practical and cost-effective whole-genome fingerprinting tool. DArT has three key attributes of interest to plant breeders and scientists studying and managing genetic diversity: (a) it is independent from DNA sequence, (b) the genetic scope of analysis is defined by the user and easily expandable, and (c) the method provides for high throughput and low-cost data production. The principle of DArT is presented in Figure 14. 1.



The genotype of an individual is determined by **detecting the presence or absence of the polymorphic fragments** in a genomic representation from that individual. This is achieved by hybridizing the genomic representation to a microarray containing copies of the polymorphic sequences.

Figure 14.1. Principle of DArT.

Sequence independence

The discovery of polymorphic DArT markers and their scoring in subsequent analysis does not require any DNA sequence data. This makes the method applicable to all species, regardless of how much DNA sequence information is available for that species. However, DArT markers are sequence-ready clones of genomic DNA.

Genetic scope

For each species, the method is developed on the "metagenome," the pooled genomes from the germplasm of interest to the user. For example, the metagenome may include DNA from the cultivated varieties of a particular region or the lines used in a breeding program. Alternatively, the metagenome may cover the genetic diversity within the entire species and even extend to its wild relatives. Importantly, the diversity surveyed by DArT can be expanded if new individuals with marked genetic differences are incorporated into the analysis at a later stage.

High-throughput, low-cost data production

In DArT, several hundred polymorphic markers are identified in parallel. The efficiency of this marker discovery effort is only dependent on the level of genetic diversity within the species. For example, 5-10% of wheat and barley DArT clones and 25-30% of cassava DArT clones were polymorphic. The same platform is used for both discovery and scoring of markers, therefore no assay development, apart from consolidating all polymorphic markers into a single genotyping array, is required after the marker discovery. The microarray platform we currently use enables a high level of multiplexing: approximately 5000-8000 genomic loci are typically surveyed in parallel in single-reaction assays to discover polymorphic markers. For routine genotyping, several hundred markers are typed in parallel using only 50-100 ng of genomic DNA. We project that our data production service will soon deliver data for less than US$0.10 per data point.

DArT markers

A DArT marker is a segment of genomic DNA, *the presence of which* is polymorphic in a defined *genomic representation* (see Figure 14.1). DArT markers are biallelic and behave in a dominant (present vs absent) or co-dominant (2 doses vs 1 dose vs absent) manner.

Identification of polymorphic DArT markers

To identify the polymorphic markers, a *complexity reduction method* is applied on the metagenome, a pool of genomes representing the germplasm of interest (Figure 10.1). The genomic representation obtained from this pool is then cloned and individual inserts are arrayed on a microarray resulting in a “discovery array.” Labeled genomic representations prepared from the individual genomes included in the pool are hybridized to the discovery array. Polymorphic clones (DArT markers) show variable hybridization signal intensities for different individuals. These clones are subsequently assembled into a “genotyping array” for routine genotyping.

Complexity reduction methods

Many complexity reduction methods can be used (Jaccoud *et al.*, 2001; Peng *et al.*, 2002). A suitable complexity reduction method produces genomic representations that are sufficiently large and contain a sufficient fraction of polymorphic clones to enable the production of a genotyping array containing several hundred markers. Our

currently preferred method is based on digestion of genomic DNA with P*st*I and a frequent cutter, followed by ligation of an adapter to the P*st*I ends and amplification of PstI fragments using a primer complementary to the adapter. This method was shown to work well in barley, a species with a 5000-Mbp genome (Wenzl *et al.*, 2004).

Genotyping by hybridization

For each individual DNA sample being typed, a genomic representation is prepared using a defined complexity reduction method. The representation is labeled and hybridized to a genotyping array, and a microarray printed with copies of the DArT markers. The hybridization signal for each marker is measured and converted into a score.

Technical platform

The platform we are currently using to discover and score polymorphic markers comprises a standard molecular biology laboratory, a microarray printer and scanner, and computer infrastructure to analyze, store, and manage the data produced. Platforms other than printed microarrays – for example color-encoded beads or self-assembling arrays - could be used for the routine typing of samples. These platforms offer good opportunities to reduce further the cost of routine genome profiling.

Software

We have written DArTsoft, a dedicated software for automatic data extraction, which is capable of producing up to 200,000 scores from discovery arrays in less than two hours (Cayla *et al*., in preparation). With this sort of throughput, sample tracking and data management become essential. We are building DArTdb, a laboratory information management system for barcode-facilitated sample tracking, data storage, and data management (Uszynski *et al.*, in preparation). As a matter of principle we only use Open Source components for all our DArT-related software products.

Current Status of DArT Development

In the last 4 years, we have established the proof of concept of DArT (Jaccoud *et al.*, 2001), and we have developed the technology for a range of species. A list of species we are currently working on is given in Table 14.1, with the number of clones we have assayed from each species, to identify the best complexity reduction method for each species.

Table 14.1. Ongoing DArT projects in different species.

Species	No. representations tested	No. clones assayed
Rice	14	26,112
Barley	10	21,504
Wheat	5	14,592
Apple	3	1,920
Cassava	4	9,216
Perennial rye grass	5	5,376
Pigeon pea	4	5,376
Sorghum	2	1,536
Fungal pathogens of barley	4	5,376
Arabidopsis	1	1,536
Mouse	2	1,536
Bovine	2	1,536
Sheep	5	3,840

Mature stage

Our work on barley has resulted in the identification of approximately 1000 polymorphic markers from two different genomic representations. A DArT genetic map has been built for a population derived from a cross between cultivars Steptoe and Morex (Wenzl *et al.*, 2004). We are now in a position to deliver whole-genome profiles of barley. Similarly, we have identified several hundred DArT markers in rice, and we are developing a genotyping tool in collaboration with the Australian rice industry.

Establishment stage

We are currently establishing the technology on wheat, cassava, apple, pigeonpea, and sorghum, in all cases in partnership with interested users. Together with colleagues from Plant Research International we also established DArT for the model species *Arabidopsis thaliana* (Wittenberg *et al.*, 2004).

Applications of DArT Markers

DArT markers can be used as any other genetic marker. With DArT, comprehensive genome profiles are becoming affordable for virtually any crop, regardless of the level of molecular information available for the crop. We anticipate that DArT genome profiles will be used for the recognition and management of biodiversity, for example in germplasm collections. Identification of duplicate accessions and a better understanding of the genetic relationships between the accessions could help to control the costs of maintaining these collections.

In plant breeding, DArT genome profiles will enable breeders to map QTL in one week, thereby allowing them to focus on the most crucial factor in plant breeding: reliable and precise phenotyping. Once many genomic regions of interest are identified in many different lines, DArT profiles accelerate the introgression of a selected genomic region into an elite genetic background (for example by Marker Assisted Back Crossing). Furthermore DArT profiles can be used to guide the assembly of many different regions into improved varieties. For that purpose, dense genome cover is essential in order to follow many regions simultaneously. Because of the large number of lines to be typed, high throughput and affordability are critical factors in this context.

A New Model for Technology Delivery

We believe that the social and environmental benefits of applying DArT could be quite substantial in developing countries, both as a result of accelerated plant breeding and better management of biodiversity. We are keen to see these benefits bring profit to users, but we also realize that developing DArT for the hundreds of species will require substantial resources. We will first explain why we think the "classical" path for the delivery of biotechnological inventions appears to be unable to deal with the peculiarities of a diverse and decentralized agricultural sector. We will then present our vision for the continuing improvement and the delivery of DArT.

In developing countries, agriculture encompasses subsistence farming that is not integrated in the global economy. In many industrial countries, agriculture is often a subsidized activity, with low economic margins. Although agricultural research results in large socioeconomic benefits (Alston *et al.*, 2000), the benefits are not easily captured by the private sector. For this reason it is becoming more difficult to attract venture capital in agricultural R&D. Early investors in agricultural biotechnology ("ag-biotech"), mostly agrochemical companies, tried to ensure a return on investment by appropriating the tools of innovation as well as its products. They used the same intellectual property (IP) protection mechanisms as in biomedical biotechnology. This left only a handful of multinational companies able

to operate in this field, and certainly contributed to the negative public perception of agbiotech in Europe and elsewhere.

We believe that other models are more appropriate for agriculture. Rather than denying access to technologies as a way to realize their value, it may be possible to develop a framework of open access to the tools of innovation (O'Neill, 2004). Janet Hope's web site at the Research School of Social Sciences of the Australian National University presents this open access concept for biotechnology in great detail: rsss.anu.edu.au/~janeth/home.html.

We have initiated the establishment of a network of DArT users, who will contribute their scientific expertise and resources to develop and improve the technology further. Key requirements to join the network are:

- Willingness to share improvements.
- Acceptance that financial rewards from the delivery of DArT services will not be derived from access to protected IP but from providing efficient "value for money" services to customers.

The growing success of the Open Source model in the software industry may provide some guidance toward establishing a sustainable system for open access biotechnology, where competition would take place, and profits would be made at the level of products and services. In this context, we hope that providing DArT services will be a sustainable activity for our organization and its partners, allowing us to develop and deliver improved genome profiling methods and to apply them to biological research and crop improvement.

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References

Alston, J.M., C. Chan-Kang, M.C. Marra, P.G. Pardey. and T.J. Wyatt. 2000. A Meta-Analysis of Rates of Return to Agricultural R&D: Ex Pede Herculem? Research Report 113, International Food Policy Research Institute, Washington, D.C.

Bonnett, D.G., G.J. Rebetzke, and W. Spielmeyer. 2004. Strategies for efficient implementation of molecular markers in wheat breeding. Molecular Breeding, in press.

Conway, G. 1999. The Doubly Green Revolution: Food for All in the Twenty-First Century. Cornell University Press, Ithaca. N.Y.

Jaccoud, D., K. Peng, D. Feinstein, and A. Kilian. 2001. Diversity arrays: a solid state technology for sequence information independent genotyping. Nucleic Acids Research, 29(4), e25.

Li, Z.K., B.Y. Fu, Y.M. Gao, J.L. Xu, C.H.M. Vijayakumar, J. Ali, R. Lafitte, A. Ismail, S. Yanagihara, M.F. Zhao, J. Domingo, R. Maghirang, F.Y. Hu, and X. Q. Zhao. 2003. Discovery and exploitation of "hidden" genetic diversity in germplasm collections for genetic improvement of abiotic stress tolerances in rice. XIX International Congress of Genetics, Melbourne 6-11 July 2003, www.genunet1.org/IGC2003/abstracts/30MinSpeakers-HTML/Li,%20Zhi-Khang.htm

O'Neill, G. 2004. Open-source biology (interview of Richard Jefferson), Australian Life Scientist, February 2004, 14-15. www.cambia.org.au/downloads/Biotechnology_News_Dec_03.pdf

Peleman, J.D., and J.R. van der Voort. 2003. Breeding by design. Trends in Plant Science, 8(7), 330-334.

Peng, K.M., D. Jaccoud, D. Kudrna, Y.G. Cho, and A. Kilian. 2002. Diversity Array Technology (DArT) applications to plant and animal genomics. Plant and Animal Genomes X Conference, San Diego, 12-16 January 2002, www.intl-pag.org/pag/10/abstracts/PAGX_W180.html

Ribaut, J.M., and D.A. Hoisington. 1998. Marker-assisted selection: new tools and strategies. Trends in Plant Science 3, 236-239.

Wenzl, P., J. Carling, D. Kudrna, D. Jaccoud, E. Huttner, A. Kleinhofs, and A. Kilian. 2004. Diversity Arrays Technology (DArT) for whole genome-profiling of barley. Proc. Natl. Acad. Sci. U S A 101(26), 9915-9920.

Wittenberg, A.H.J., A. Kilian, and H.J. Schouten. 2004. DArT™, a promising genetic fingerprinting technology. Plant and Animal Genomes XII Conference, San Diego, 10-14 January 2004. www.intl-pag.org/12/abstracts/W36_PAG12_168.html

Xiao J., J. Li, S. Grandillo, S.N. Ahn, L. Yuan, S.D. Tanksley, and S.R. McCouch. 1998. Identification of trait-improving quantitative trait loci alleles from a wild rice relative, Oryza rufipogon. Genetics 150(2), 899-909.

Section 4

Agrobiodiversity and the Environment

Chapter 15

Agrobiodiversity, People, and the Environment

Mahmoud Solh, Peter Kenmore, and Jasmine Hyman

Introduction

Despite the global consensus that hunger must end, the numbers of hungry people are still rising. Progress in fighting hunger, notable in some areas, is slow and uneven. According to FAO estimates, well over 800 million people are chronically undernourished. This figure represents 17% of the population of the developing countries, up to 34% in sub-Saharan Africa, and even more in some individual countries (FAO, 2003b).

FAO (2003a) indicates that the growth rate of world population, which had peaked in the second half of the 1960s, is decreasing, and the world population is projected to be 9.3 billion in 2050. Considering that the standard of living is generally increasing worldwide, this population will require additional food production equivalent to an increase of about 60% of the current levels.

At the same time, natural resources–particularly land and water resources–are under increasing competition for nonagricultural use as industrialization and urbanization expand. FAO (2003a) estimates that 36% of the world's land is, to some degree, suitable for crop production, and that of this amount only 11% (1.5 billion hectares) is actually used to grow food. However, the remaining 2.7 billion hectares of arable land is under increasing pressure for industrial and urban use. Much of the remaining land also suffers from ecological fragility, low fertility, salinity, toxicity, high incidence of disease, or lack of infrastructure. It therefore requires high investments for agricultural production, and most significantly, regions that need land may not have it–the available arable land being unevenly distributed.

Agricultural Intensification and its Implications

A strong correlation exists between countries that achieve significant increases in agricultural development and countries that make significant progress toward eradicating hunger and poverty to meet the Millennium Development Goals (MDGs). Agricultural development can occur "horizontally," that is, development by expanded land area devoted to agriculture, or "vertically," that is, development via intensified production and increased output per hectare. Horizontal agricultural expansion is not a viable option for most regions, given land limitations and other resource constraints within developing countries; there is also a need to concentrate agricultural development within the localities that are the most food insecure.

Vertical expansion of agriculture, or production intensification, will therefore be responsible for 80% of the future increase in food production required (FAO, 2003a). However, environmental pressures from intensification of land use are projected to increase steadily over the next 20 years. In the past, intensification has been faulted with gradually degrading natural resources such as land, water, forests, biodiversity, air, and climate. Agricultural intensification can be made more sustainable and less damaging to natural resources through better understanding of agrobiodiversity and agro-ecosystems, proper applications of new technologies and scientific innovations, and appropriate policies.

Understanding Agrobiodiversity and Agroecosystems

The first step in understanding how to intensify and protect agricultural systems is to refine human knowledge of the natural biological processes that support and maintain these systems. According to Article 2 of the Convention on Biological Diversity (CBD) "biological diversity means the variability among living organisms from all sources including ... diversity within species, between species and of ecosystems." We focus on the sustainable use of "agricultural biodiversity," which encompasses genetic resources for food and agriculture, components of agricultural biodiversity that provide ecological services, abiotic factors, and socioeconomic and cultural dimensions (Convention on Biological Diversity, 1994).

Agrobiodiversity is centered on the crops, animal breeds, forest varieties, fish, honeybees, and other harvested species that exist and persist only because human beings have consciously selected them, protected them, and transformed landscapes to host them. Agrobiodiversity secondarily includes nondomesticated species that humans have indirectly selected, like weeds, which are plants that grow in human-constructed agro-ecosystems voluntarily. Other secondary sources of agrobiodiversity include pests and their natural enemies, which might have come to exist without recurrent human intervention, but certainly would not then be found in the densities and geographic ranges that now characterize them. Agronomists should further promote and foster agrobiodiversity to capitalize on its functions and services.

Agrobiodiversity functions within agricultural systems to provide food, fiber, raw materials, and shelter. It also performs essential ecosystem services such as: nutrient cycling, carbon sequestration, pollination, moderation of climatic effects, environmental stability, and pest control. Supporting and encouraging agrobiodiversity is the key element in ensuring that an agricultural system is sustainable.

Applications of Technologies and Innovations

Science is a double-edged sword. Although global challenges of promoting agrobiodiversity and sustainable agricultural intensification have benefited from scientific advances in the past decade, science and technology can also have negative impacts. Like any other tools, what matters is who uses them, and how. These advances, however, too often automatically promote technological approaches without looking at the importance of ecological understanding, community empowerment, education, and policy reform. This blind approach is much like a doctor prescribing medicine to an unseen patient.

Farmers, producers, consumers, extension workers, civil society, scientists, policymakers, government representatives, private companies, and international organizations must be empowered with scientific knowledge of ecosystems to implement innovative technologies successfully. For example, the responsible use of plant biotechnology can provide solutions to problems for which conventional technologies have failed, or enhance the efficiency of conventional breeding methods. Modern biotechnology can give scientists molecular tools such as genomics for better understanding the structure and function of genes in living organisms. Genetic engineering is a technique that allows genes to be transferred from one species to another. It leads to the production of genetically modified organisms (GMOs). Overcoming the species barrier is what gives genetic engineering tremendous power, but makes it so controversial. Unfortunately, GMOs mask other important biotechnological tools including genomics, tissue culture, cloning, and molecular markers (among others), which may be harnessed to benefit particular agricultural systems with particular needs (Solh *et al.*, 2003).

The use of Geographic Information Systems/Remote Sensing (GIS/RS) for early warning and response to locusts and other agricultural hazards also exemplifies responsibly applied science. Modern assessment methods such as the agroecological zoning (AEZ) methodology can invaluably assist land resource inventory, land suitability and land productivity evaluation (including forestry and livestock productivity). AEZ can also assist in population-supporting capacity assessment and land-use optimization modeling, as well as the assessment of the impact of climate change in addition to many other applications. Information technology and expert systems may also be used as a tool in technology transfer for intensified agriculture production.

However, the inappropriate use of technologies, for example excessive chemical or pesticide use, can have dramatically harmful environmental effects due to increased pesticide resistance and reduced agrobiodiversity leading to genetic vulnerability. Agricultural disasters such as Ireland's potato famine in 1845-1850, the Southern Corn Leaf Blight in the United States during the 1970s, and the Faba Bean Necrotic Yellow Virus outbreak in Central Egypt in 1991-92 were all directly caused by increased genetic vulnerability due to reduced agrobiodiversity. Solutions for intensified production are myopic and potentially disastrous if their application compromises agrobiodiversity.

Enabling Policies for Sustainable Agriculture Intensification

Given that natural resources do not respect state boundaries, a vast majority of multilateral international agreements were created to protect and manage common resources such as land, water, and air quality. National policies are guided by international accords such as the International Treaty on Plant Genetic Resources for Food and Agriculture; International Plant Protection Convention; Rotterdam Convention on Prior Informed Consent; Agreement on the Application of Sanitary & Phytosanitary Measures (SPS); Cartagena Protocol on Biosafety; Codex Alimentarius; and FAO Code of Conduct on Pesticides. In addition, international conventions affecting agrobiodiversity and technology include the "Earth Summit" of 1992 in Rio de Janeiro, the United Nations Framework Convention on Climate Change, the United Nations Convention on Biodiversity, and others.

In addition to international accords, local empowerment and ownership are essential for sustainable natural resource management. Education will make the expertise to solve new problems arising from environmental change available when and where needed. Policy reforms to change existing incentives will promote environmentally friendly choices.

The triumvirate of agrobiodiversity understanding, appropriate technologies, and enabling policies has the potential to overcome the global challenge to achieve sustainable food intensification. A brief analysis of varied case studies in the West Asian and North African dryland region, the Asian rice agroecosystems, a Madagascar forestry project, and a Costa Rican biodiversity project illustrates the cross-cultural importance of the "triumvirate" to enhance agriculture productivity and livelihood, as well as sustain the natural resource base on which future generations will depend.

Development of Integrated Crop-Livestock Production in Low Rainfall Areas

A successful case study that joins scientific advances with enabling and responsible policies for intensified agricultural production comes from the dryland regions of Algeria, Iraq, Jordan, Lebanon, Libya, Morocco, Syria, and Tunisia. The combined population of the Mashreq (Iraq, Jordan, Lebanon, and Syria) and Maghreb (Algeria, Libya, Morocco, and Tunisia) was over 116 million in 1997 and is expected to increase to 175 million by 2020. Approximately 36% of the population live in rural areas, and agriculture employs over 30% of the labor force. Although an increased percentage of this population is expected to migrate to urban areas in the future, the absolute number of people dependent on agriculture for their livelihoods is increasing.

In addition, the region has strained agricultural resources. Only 22% of the region's total land area is classified as agricultural, of which 70% is used as permanent pasture. Low rainfall and delicate soil conditions further constrain agricultural production. In short, the region contains limited agricultural land for an expanding population, with high dependency on agriculture for its livelihood; the Mashreq/Maghreb area is a prime candidate for vertical agricultural expansion (Haddad and El Tom, 2002).

The Mashreq/Maghreb Project focuses on integrating crop/livestock production systems in the low-rainfall areas of West Asia and North Africa. It is a joint effort by the national programs of the countries involved, the International Center for Agricultural Research in the Dry Areas (ICARDA) and the International Food Policy Research Institute (IFPRI). The project has been supported by the International Fund for Agricultural Development (IFAD) and the Arab Fund for Economic and Social Development (AFESD).

The following discussion is largely derived from the project's final report to IFAD, (Haddad and El Tom, 2002). The project was conceived to combat socioeconomic imbalances within the region's rural communities originating from successive droughts, demographic pressures, and centrally planned production and marketing within the participating nations. The main objective of the project was to realize a sustained increase in productivity, incomes, and livelihoods of the small and marginalized crop and livestock producers by introducing new, simple, and innovative technologies. The technologies were closely integrated with and supported by community participation and policy reforms, with particular emphasis on land tenure, land use, and improved marketing and credit systems.

The project achieved notable signs of success in every country. Briefly, improved barley varieties in Iraq achieved a 19% yield advantage over the local variety; Jordan achieved a 93% adoption rate of improved barley cultivars, in addition to a 28.8% adoption rate on new technologies and methods for livestock production (early weaning) and the use of food blocks (21%). Similarly high adoption rates of improved barley varieties were achieved in Lebanon (roughly 66%), and Syria achieved a barley yield gain of 20% after participation in the project.

The salient feature of the project was a high-level commitment to rural participatory approaches when implementing the technological packages. The packages themselves were selected by ICARDA and IFPRI, organizations with scientific expertise; however the success of the project certainly lay in its ability to transfer this expertise to local people. According to ICARDA (2000), the problems facing the region could be solved by "neither technical interventions nor policy adjustments alone." The project "integrated research on technologies and management practices with research on policy and institutional alternatives so as to provide the policy and institutional support for wider adoption of improved production and resource management practices." The project coupled state-of-the-art science with regional cooperation, national activity, and local capacity building through extension services, farmer training, and workshops for rural communities (ICARDA, 2000).

Asian Rice Systems

In Asia, rice agroecosystem analysis was first conducted by researchers in the 1970s and now has been taken up by over one million participants in Farmers' Field Schools. Rice paddies are the most intensive and diverse agricultural ecosystems that have been associated with important civilizations in the early history of agriculture. Rice-based systems, in addition to producing rice, are associated with the production of livestock, fisheries, and ducks. Even rice "monocultures" are remarkably diverse as they draw components from associated freshwater ecosystems and may contain 1000 arthropod species per hectare (per 10 tonnes of standing plant biomass). Notably, the biodiversity within a rice system is roughly the same ratio as tropical rainforests: 10,000 to 15,000 species per 400 tonnes of tropical rainforest.

According to a 1996 Indonesian field study on rice ecosystems conducted by FAO and the Indonesia National Integrated Pest Management Program (IPM) on Java, previous misunderstanding of biodiversity within rice systems had led to counterproductive insecticide use. The findings are particularly noteworthy given that in 1990, "worldwide, rice now accounts for more pesticides than any other crop, with about 80% of this amount used in Asia" (Woodburn 1990 cited in Settle *et al.*, 1996).

The study sampled biodiversity within the "organic soup" that occurs at the ground level of a flooded rice field, and determined that organic matter residues from the previous crop cycle, algae, and organic wastes from village irrigation waters support bacteria, phytoplankton, which further support zooplankton. The study mapped secondary, tertiary and higher level predators and demonstrated that this web–undisturbed–will naturally provide a beneficial spider on every rice plant within two days of transplanting. The top layers of the rice aquatic food web are the predator species that later defend the rice paddy from pest invasions. Because the aquatic food web is driven by the decomposition of nonharvested rice and associated biomass,

preserving/increasing natural enemy populations and the organic matter on which they depend in the rice paddy, improves biological pest control and usually eliminates the need for insecticides (Figure 15.1).

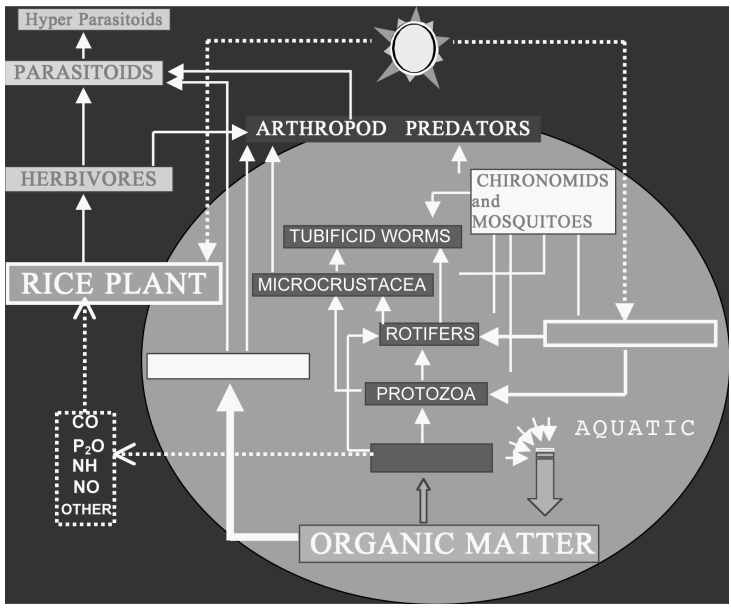

Figure 15.1. Rice and agrobiodiversity (Source: W. Settle *et al.,* 1996).

Contrary to widespread belief among scientists and policymakers during the Green Revolution, the study indicated that the early-season applications of insecticides would damage the process of rearing natural enemies to rice plant predators, and is therefore counter-productive. It recommends that farmers make decisions on insecticide use based on the relative proportions of herbivores and predators at each growth stage of their crops.

This work has since been extended beyond rice to illustrate how soil organic matter management can increase predator populations early in the crop season with better pest regulating capacity. In China, this work has been adapted by thousands of cotton farmers growing *Bt* transgenic varieties. This has further reduced insecticide applications and increased profits. In short, scientific understanding of the field's agrobiodiversity leads to intelligent management, reduced inputs, and ecological sustainability. By studying the agrobiodiversity within the rice system, the common and oversimplified prescription of "increased inputs for increased outputs" was rebutted, and the policy of supporting the natural aquatic ecosystem was endorsed. The IPM method, combined with *Bt* corn, achieved the highest commercial return with relatively minimal input (Figure 15.2).

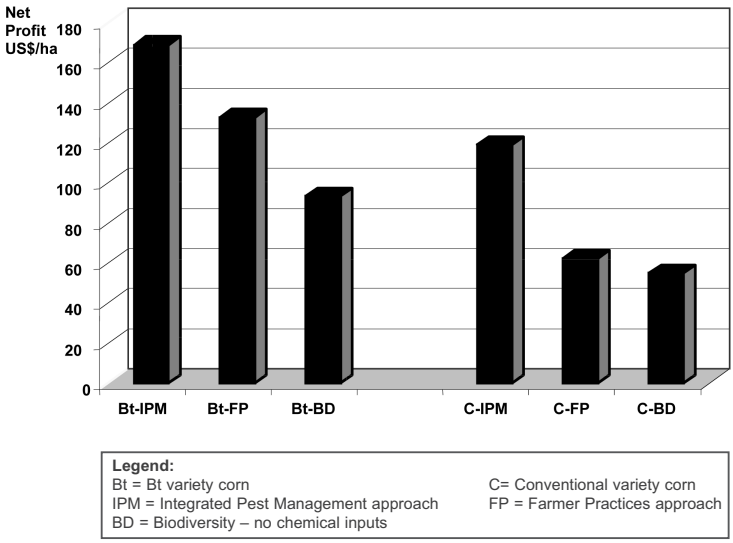

Figure 15.2. Net profits from integrated pest management in Bt and conventional cotton in China, 2002 (Source: FAO-EU, 2003).

Madagascar's Forests

In a different study with comparable implications, a participatory appraisal in Madagascar's endangered Anivorano forest highlights the need to understand the cultural backdrop of diversity-rich land before implementing policy reforms to protect it. The following discussion is derived from Schoonmaker-Fruedenberger (1995).

Madagascar, the fourth largest island in the world, is a global hotspot for biodiversity and home to nearly 8000 endemic species of flowering plants. The nation's native vegetation is currently under threat due to rapid deforestation in the name of economic development. The island's agrobiodiversity is used locally for food, medicine, fuel, shelter, and export products such as wood. Current rapid depletion of these materials is not only a matter of concern to local and national bodies, but also the international community, given the unique vegetation and genetic diversity native to the island.

Within Madagascar, the Anivorano village forest is under severe threat (currently only 20% of the village territory is forested, whereas 50 years ago it was more than 50%). At this rate, it may disappear entirely in the next 20 years. The Anivorano forest is also undergoing land titling reform. Under government supervision, it is shifting from village ownership to individual land titling. As noted by Schoonmaker-Fruedenberger (1995): "Often people assume, for example, that formal, government-supervised titling of individual land parcels will increase the holder's tenure security. It is supposed that this will, in turn, lead the titled owner to invest and intensify production on agricultural lands, thereby diminishing the practice of more extensive production practices, which put pressure on forests." However, the assumption that private land ownership will increase an estate owner's incentive to responsibly manage the land was not verified in relation to the Anivorano forest, as indicated by a Rapid Rural Appraisal study (RRA).

Using a participatory approach, researchers investigated the community of Anivorano and its livelihood, the natural resource base and the tenure and resource management systems (customary and external) that affected how the community interacts with its resources. They concluded that the forest was threatened by two intertwined forces. The first is related to the local production system and the pressures of increasing population on the resources of the territory. Anivorano depends for its livelihood on the production of rice, which is mostly grown on steep hillside slopes under a system known in Madagascar as *tavy*. In this system the slopes are cleared of vegetation and rice is planted for one year. After a fallow of five years, the land is again cleared for rice production. This cycle continues for about 50 years, during which time no more than eight or nine harvests of rice can be obtained. Even with the maintenance of five-year fallows, yields decline as the soils deteriorate over time on these hillside fields, and after 50-60 years the fields must revert to long-term fallow if they are to be used for rice cultivation again. With increases in population, decreases in yields on already cleared lands, and the allocation of barren lands to long-term fallow, there is constant pressure to clear new lands, particularly in the forested part of the village territory where soils are the richest.

The customary tenure system, based on a "covenant" passed down from the villagers' ancestors, contains numerous provisions that protect the forest by encouraging the maximum use of lands already cleared. The forest has traditionally been maintained by the local population as a "reserve of last resort" to be used only when the village is unable to produce sufficient food on lands already cleared. This policy is currently being threatened by outsiders who do not respect the customary arrangements.

The second threat to the forest comes from outside the territory. Some five years ago a road to the village was built, attracting commercial woodcutters and resulting in a confrontation between customary and state tenure systems. The State insists that the forest that was claimed by Anivorano residents as part of their territory (according to the ancestral covenant) is actually part of the national domain. This means that the government does not recognize the local inhabitants' rights to manage

these lands as part of their territory. The State has granted permits to commercial logging interests, which have begun to cut large swaths through the forest. The result has been not only the anarchic cutting of valuable old trees and the destruction of the forest cover, but also the serious weakening of Anivorano's customary tenure system as the local population watches outsiders exploit “their” resources with impunity. This is leading to a breakdown in the covenants controlling the villagers' use of the forest for *tavy*. Increasingly, the local inhabitants are violating customary rules and clearing the forest for agriculture–just the opposite of what the State intended by claiming the land as national domain.

Schoonmaker-Fruedenberger’s (1995) study looks at both policy measures and local development actions that will be needed to slow the destruction of the Anivorano forest. Since Madagascar, with the encouragement of some donors, is currently considering the reinstitution of a national policy of land titling, the study considers the impact that such registration of private lands might have on tenure security in the area. It concludes that while territorial titling in the name of the community may be a useful element in protecting the forest by reinforcing the customary tenure system, individual titling of private parcels (the system currently being promoted) would probably be counterproductive and possibly lead to even more rapid destruction of the vegetation.

In any case, no policy measures will be sufficient unless care is also taken to address the internal pressures on the forest resulting from population increases and declining agricultural yields on tavy fields. The Anivorano forest is an elegant example of the need to work within cultural systems, and to respect traditional “covenants” when creating policies to curb the environmentally degrading effects of rapid population growth, resource demand, and economic development.

Managing Costa Rica’s Biological Riches

Costa Rica hosts an extraordinary wealth of natural diversity. Within about 51,000 sq km, the country is home to nearly 5% of the world’s diversity, with an estimated 500,000 species of animals, plants, and microorganisms. Costa Rica is also exceptional in that, as a developing country, it has achieved life expectancy, quality of life, health, and literacy indicators comparable to fully industrialized countries (Gamez, 2003).

The National System of Conservation Areas protects 25% of all national land, depending on land estimate methodology. In addition, Costa Rica’s ecotourism industry is well developed and generated US$1,249 million in 2000, or 9% of GDP. Gamez (2003) examined the foreign exchange generated by ecotourism, as compared with the foreign revenue procured through select agricultural activities. Biodiversity conservation has been the most productive income generator in the country.

In accordance with Costa Rica’s current strategy for development, conserved land will expand to cover one-third of the nation, leaving 15% of the nation’s land available and suitable for agricultural development. It is therefore necessary for

Costa Rica to intensify agricultural production to meet the needs of its growing population and ambitious development agenda. According to analysis by Sittenfeld *et al.,* (2003), agrochemical inputs increased tenfold between 1990 and 1996; however, the increase in crop yields per hectare was not significant in relation to the level of increased inputs.

Pesticide and agrochemical use has poisoned an increasing number of field workers and threatens the ecological health of agricultural land. The Costa Rica model is particularly compelling because it begs the question: "Does conservation of natural reserves force over-intensification of agriculture on the remaining available land?" Costa Rica may either continue with the unsustainable and ineffective use of agrochemicals or it may seek alternative solutions through science (Table 11.1).

Sittenfeld *et al.,* (2003) highlight the "Rice Biotechnology Program" as a potential solution to sustainable agrointensification. Approximately 25% of daily caloric intake comes from indica rice varieties, the rice species native to Asia. The rice *hoja blanca virus* disease (RHBV) is endemic to tropical America, and therefore indica rice varieties have no natural resistance. Costa Rica is currently experimenting with nonconventional breeding strategies to increase resistance to the virus. The Rice Biotechnology Program of the Centro de Investigacion en Biologia Celular y Molecular (RBP-CIBCM) is conducting this research. As the first locally produced transgenic crop that addresses production constraints not considered by private and public research institutions in industrial countries, the RBP-CIBCM is facing many challenges. Costa Rica, with its longstanding commitment to environmentally friendly development techniques, is subjecting the RHBV-modified rice to vigorous testing models, health and environmental risk assessment, and management of transgenic crop under tropical conditions analysis.

Although the crop has not yet completed regulatory requirements, the development of a nonconventional rice plant may be appropriate given that Costa Rica has limited land for agriculture and that agriculture development is one of its most important economic sectors. To avoid farmland depletion due to ineffective and noxious chemical inputs, alternative methods of intensification should be studied with a keen eye toward careful implementation in the long term.

Costa Rica is now reviewing its national conservation system to select wisely protected areas and foster ecotourism for appropriate production management, along with advanced technologies to ensure sustainable agriculture development for food security and adequate national income.

Table 15.1. Protected Land, Chemical Input and Yield in Costa Rica.

	Before high input	**After high input**
a. Protected Land and Chemical Input in Rice Production		
	1991	1996
Protected Area	1,094,414	1,602,420
Total agrochemical imports (thousands of kg or liters)	274,040	543,348
Pesticides	6,438	60,886
Fertilizers	267,271	458,149
Other	330	2 4,313
a. Protected Land and Chemical Input in Rice Production		
	1984-1991	1992-1999
Rice harvested area (ha)	66,423	60,000
Production (t)	217,520	229,251
Yield/area (t/ha)	3.26	3.87

Sources: a. PROCOMER, 1997 and Estado de la Nación, 1997. Courtesy of Sittenfeld (2003); and b. Servicio de Información de Mercados, Dirección de Mercadeo Agropecuario, CNP, 1999. Area, Production and Yield per area represent averages. Courtesy of Sittenfeld (2003).

Conclusion

The significance of the four case studies is that agricultural intensification and agrobiodiversity conservation are not necessarily mutually exclusive goals. Harm is caused when policymakers apply "common sense" to agriculture systems without considering the socioeconomic factors, and the traditional resource management systems, or without sufficient understanding of the biodiversity involved. Using pesticides in the Indonesian flooded rice system–despite the commonly accepted idea that "increased inputs mean increased outputs" was counterproductive. Studying and understanding the complex web of natural predators and their biological support system led to improved rice production with fewer inputs--a win-win situation.

In Madagascar, applying the "common sense" theorem that private titling translates into more responsible land use, undermined the traditional village system that had intrinsic mechanisms for protecting natural diversity. Villagers must adjust to increasing pressure on their resources due to population growth and economic progress. Policymakers need to explore counter-incentives to protect the forest according to the cultural/traditional system already in place.

Similarly, in Costa Rica where agricultural land is voluntarily limited due to a heightened national awareness, policymakers fell prey to the "intensify agriculture with intensified inputs" premise. While this assumption may indeed be correct in some cases, it was counter effective on Costa Rican fields. Alternative approaches, such as using tailored science for Costa Rica's local needs and local problems, may prove to be a more effective approach to agricultural intensification and sustainable development. The technological solution here is locally conceived and produced.

As exemplified in the West Asia and Northern Africa dryland region, a suite of collaborative mechanisms can move sustainable agricultural intensification from the conference hall to the field. Regional collaboration helped extend national policies to move scientific innovations to rural people. A focus on rural training, farmer field schools, and locally adapted approaches toward the new technologies transformed a difficult agricultural region into a success story.

Agriculture intensification per unit area, if practiced in a nonsustainable manner, is certainly a serious threat to agrobiodiversity. However, scientific advances, if used properly, can meet global challenges of conservation of agrobiodiversity and sustainable agriculture intensification. People may misuse scientific advances. Far too often these advances are applied automatically to promote technological approaches without looking at the importance of sustainability, socioeconomic conditions, community empowerment, education, and policy reforms. The World Food Summit targets and Millennium Development Goals, which fight hunger and poverty and protecting the natural resource base, including agrobiodiversity, can be met through sustainable agricultural development based on scientific advances, in addition to farmer and community empowerment, and an enabling policy environment.

References

Convention on Biological Diversity. 1994. Scope of Agricultural Biodiversity appendix, available from < http://www.biodiv.org/decisions/default.aspx?m=COP-05&id=7147&lg=0> [Accessed 15 July 2004].

Food and Agriculture Organization (FAO). 2003a. World Agriculture: Towards 2015/2030 An FAO Perspective. Rome.

FAO. 2003b. State of Food Insecurity Report. Rome.

FAO-EU. 2003. Regional Programme for Cotton IPM Training and Development in Asia. Rome.

Gamez, R. 2003. The Link Between Biodiversity and Sustainable Development: Lessons from INBio's Bioprospecting Program in Costa Rica. In: Conference on "Biodiversity, Biotechnology, & the Protection of Traditional Knowledge" held at Center for Interdisciplinary Studies and the Harris Institute for Global Legal Studies at the Washington University in St. Louis <http://law.wustl.edu/centeris/pastevents/> [accessed 15 July 2004].

Haddad, N., and A. El Tom. 2002. TAG No. 385- ICARDA: Programme for the Development of Integrated Crop-Livestock Production in Low Rainfall Areas of Mashreq and Maghreb, Phase II: Participatory Validation of Integrated Systems Technology Packages to Improve Adaptability under Favorable Policy Environments. Completion Review Mission (CRM). Rome, submitted to International Fund for Agricultural Development.

ICARDA. 2000. Integrating Crop/Livestock Production Systems in the Low-Rainfall Areas of West Asia and North Africa: The Mashreq/Maghreb Project. ICARDA, Aleppo, Syria.

Schoonmaker-Fruedenberger, K. 1995. Tree and Land Tenure: Using Rapid Rural Appraisal to Study Natural Resource Management: A case study from Anivorano, Madagascar. FAO, Rome.

Settle, W.H., H. Ariawan, E. Tri Astuti, W. Cahyana, A. Lukman Hakim, D. Hindayana, A. Sri Lestari, and Pajarningsih. 1996. Managing Tropical Rice Pests through Conservation of Generalist Natural Enemies and Alternative Prey. Ecology, 77(7): 1975-1988.

Sittenfeld, A., A.M. Espinoza, and G. Arrieta. 2003. Costa Rica: Biodiversity and Biotechnology at the Crossroads. In: Conference on "Biodiversity, Biotechnology, & the Protection of Traditional Knowledge" held at Center for Interdisciplinary Studies and the Harris Institute for Global Legal Studies at the Washington University in St. Louis <http://law.wustl.edu/centeris/pastevents/ > [accessed 15 July 2004]

Solh, M., A. Impiglia, and A. Maddur. 2003. Science and Technology Strategies and Policies for Enhancing Food Security and Sustainable Development in North Africa. In: "North Africa Workshop: Study on Science and Strategies for Improved Agricultural Productivity and Food Security in Africa" held at Inter Academy Council and AARINENA, Rabat, Morocco, 2-6 February 2003 (anticipated publication by FAO, Rome).

Chapter 16

Agricultural Biodiversity for Sustainable Development: Strengthening the Knowledge Base

J. Thompson, C. Hoogendoorn, and T. Hodgkin

Introduction

Crop output worldwide must rise two-fold in the next 20 years just to keep up with human population growth (Imperial College, Wye, 2003). This increase must occur–and be sustained–in the face of climate change, increased urbanization and demands for agricultural lands by growing cities, competition for scarce natural resources, and possible continuing global conflict. The methods adopted must be ecologically sustainable and ensure improved livelihoods for farmers in developing countries. Ways will be needed of increasing production and productivity that do not increase vulnerability of farmers and agricultural systems, and are profitable for farmers.

One of the essential elements for meeting these challenges lies in the diversity present in agricultural production systems. For crops, this includes both the diversity of crops that are produced and the genetic diversity present within crops. Only 15 major food crops provide more than 90% of the calorie intake of humans worldwide, and human nutritional needs require a much wider diversity. The increasing marginalization of nutritionally beneficial crop species in favor of dependence on a few staples will need to be reversed. Genetic diversity present within crops and their close relatives has provided, and will continue to provide, the basis for increased productivity, increased resistance to pests and diseases, and resilience to abiotic stress.

This diversity is under threat as crop varieties adapted to specific environments, and with them the genes and alleles they carry, are subject to erosion and extinction. Over the past 50 years, genetically uniform crop varieties have replaced many thousands of landraces over huge production areas. These monocultures have resulted in high and uniform yields, but they can be highly vulnerable to emerging pests and diseases, as in the case of the southern leaf blight epidemic of maize in

1970 (National Research Council, 1972) or the recent loss of chickpea production in Australia (Anthony Gregson, pers. com). Estimates of rate of loss of diversity are difficult to obtain, but FAO has suggested that three-quarters of the original varieties of agricultural crops have been lost from farmers' fields since 1900 (FAO, 1998). The consequences of declining crop diversity and genetic diversity are likely to include an increase in farmers' vulnerability, a reduced capacity to improve productivity and respond to changed production circumstances, in other words in a decrease in agroecosystem resilience and adaptability.

Agricultural biodiversity(1) provides an insurance policy against production failure, the basis for optimum use of land and other nonbiological resources, and a means of adapting to change and increasing productivity. It also is essential for a wide range of ecosystem services through nutrient cycling and regulation of key processes such as carbon sequestration. IPGRI and other CGIAR centers work on many different aspects of biodiversity, and are involved in global programs on the maintenance of crop, livestock, forestry, and aquatic diversity. The centers pursue *ex situ* and *in situ* conservation, optimum maintenance, and use of soil biodiversity (CGIAR, 2003). Key aspects of the improved maintenance and use of agricultural biodiversity are addressed, through such areas as integrated pest management and work on pollinators. We focus here on the need to develop an improved knowledge basis to support the optimum maintenance and use of agricultural biodiversity in sustainable production. The value and importance of improving our knowledge is illustrated with particular reference to crop diversity.

Understanding Agricultural Biodiversity

Central to any effective effort to use diversity better must be adequate methods to describe its extent, distribution, and character. This must reflect both the technical and scientific aspects of diversity estimation, and the ways in which farmers describe value and understand diversity. There must also be ways of identifying change and of integrating information across ecosystems, landscapes, and systems.

Locating, measuring, and monitoring agricultural biodiversity

The fifth meeting of the Conference of Parties (COP V) to the Convention on Biological Diversity acknowledged the need for increased understanding of the underlying causes of the loss of agricultural biodiversity, and called for an integrated assessment of all its components. This would help us understand the nature, extent,

(1)Described by the Convention on Biological Diversity as the biological diversity present at all levels in the biological hierarchy from genes to ecosystems involved in agricultural production including crops, livestock, trees and interacting species of pollinators, symbionts, pests, predators and competitors.

and distribution of agricultural biodiversity as well as the threats of erosion or extinction of elements of that diversity. Progress has been made in describing and understanding the extent and distribution of genetic diversity of some of the major crops and livestock species (FAO, 1998; Doebley, 1990; Hanotte *et al.*, 2002). However, for many crop and livestock species information is still limited and our knowledge of the extent and distribution of diversity of soil biota, pollinators, and other components as well as of rates of change and factors that affect this is even more limited (FAO, 2002).

Knowledge of distribution of crop and genetic diversity and of the ways in which these are changing allows for identification of areas of potential vulnerability due to increased uniformity and for detection of potential problems for farmers and communities with respect to access to seed and nutritional diversity. It also provides the basis for planning conservation actions, essential to maintaining the long-term resource base for future production increases.

Molecular genetic methods, with geographic information systems and improved information management techniques, provide a powerful basis for developing the knowledge needed (Guarino *et al.*, 2001). Thus, comparative genomics and bioinformatics, which are areas that give added value to traditional genetic resources research programs, are central components of the recently implemented CGIAR Generation Challenge Program on Cultivating Plant Diversity for the Resource-Poor (www.generationcp.org). Research areas that need to be given increased attention include measurement of the extent and significance of gene flow in traditional seed systems, the development of indicators of diversity and diversity change, and data management and analysis.

Developments in related scientific areas have implications for strengthening the scientific basis of genetic resources conservation and use. Nanotechnology, based on the manipulation of individual atoms and molecules to build structures to complex atomic specifications, has potential use in agricultural research to support the advancement of genomics and proteomics through the *in situ* synthesis of molecules. The consequences for agriculture would be through biological treatments and through increased understanding of plant diversity in terms of cell and plant function.

Agricultural biodiversity in its human context

Farmers and communities in rural areas shape the extent and distribution of the diversity present in the plant and animal species in agricultural production systems, both directly through selection, and indirectly through management of biotic and abiotic agro-ecosystem components. Agricultural biodiversity, and the knowledge associated with it, constitutes a key asset of poor farmers, especially in marginal and difficult farming situations. The maintenance and use of diversity can thus constitute a central element of livelihood strategies in many rural communities. The experience and knowledge of these farmers collected and developed over many generations by

growing and improving and adjusting crop plants has resulted in the crop and genetic diversity that we know today.

In many parts of the world, substantial amounts of this biodiversity continue to be maintained, along with newer varieties produced by private breeders and national and international breeding programs. The seed of these materials circulates as part of the informal seed systems that are often responsible for over 90% of seed used by farmers in many developing countries (for example, Tahiri, 2004). Substantial progress has been made in understanding and supporting the maintenance of crop diversity on farms, including work on maintenance of traditional varieties (Jarvis *et al.*, 2004), the management of seed systems (Subedi *et al.*, 2003), and participatory plant breeding work (Sthapit et al, 1996). A number of initiatives have been developed that support the maintenance of the material and strengthen indigenous knowledge systems through such devices as community biodiversity registers, farmer field fora, seed diversity fairs, and drama and poetry festivals (Jarvis *et al.*, 2004). A firmer understanding is also emerging of the ways in which diversity of traditional crop and livestock types is organized within and between traditional varieties, maintained and used (Bajracharya *et al.*, 2004; Zimmerer and Douches, 1991; Louette *et al.*, 1997). A major challenge that remains is to develop adequate descriptions of maintenance and flows of diversity at the seed system level. This will permit development of improved strategies to provide materials to farmers and allow for better conservation decision-making.

Linkages between components of agricultural biodiversity

COP V of the Convention on Biodiversity emphasized in Decision V/6 (http://www.biodiv.org/decisions/default.aspx?m=COP-05&id=7148&lg=0) the importance of utilizing the ecosystem approach to investigate the linkages, synergies, and associations between different components of agricultural biodiversity (crops, livestock, fish, trees, pollinators, soil biota, pests, pathogens and symbionts, and management practices). There is firstly a need to investigate the ways in which different amounts of diversity are distributed among different components. An apparently uniform production system from a crop perspective (such as paddy rice) may have an extensive diversity of other organisms such as insect species (Settle, 2001). This will provide the necessary framework for understanding the interactions between the diversity of the different components.

Using and Conserving Agricultural Biodiversity

If we are to ensure that agricultural biodiversity makes its full contribution to improved food security, human well-being, and environmental maintenance, we need to have the knowledge required to deploy it effectively, to understand what it can contribute and to ensure that its more effective maintenance and use benefit farmers and communities.

Improving the use of diversity

Establishing an agricultural biodiversity knowledge base involves bringing to bear all the tools at our disposal, including those in the realm of biotechnology, on further defining our understanding of genetic diversity. Molecular techniques are central to many research programs aimed at identifying and utilizing useful alleles that confer adaptive advantages to crops, in terms of resistance to pests and diseases and response to changing environmental stresses (drought, flooding, increasing salinity, shortened or lengthened growing seasons), as well as socioeconomic advantages such as increased yield and improved nutritional quality.

Production stability and crop adaptability are dependent on genetic diversity and, for major crops, much of this is now conserved in genebank collections. Many valuable traits have already been incorporated from material in such collections (Plucknett *et al.,* 1987), and there is no doubt that many useful new alleles remain to be discovered (Tanksley and McCouch, 1997). As the need for readily available genetic and genomic information to use in targeted applications has grown, so has interest in and support for molecular evaluation of genebank material. Recent developments in biotechnological applications, particularly with regard to genomics and proteomics, allow a much more precise identification and definition of genes, alleles and the useful traits they underlie. With genetic marker techniques and genomic information, evaluation of useful traits and the development of improved cultivars incorporating these traits is becoming both cheaper and faster (Koo and Wright, 2003).

Other areas of investigation that contribute to the knowledge base and are subjects of current and planned research activities of IPGRI and other research institutes are the development of methodologies and strategies for improved genebank management, the implementation of high-throughput tools for germplasm characterization, the promotion of the use of wild species in breeding programs, and the definition of the genetic erosion baseline of crop species. Activities that are increasingly visible on the priority lists of researchers worldwide are:

- The development of standards of genetic marker technologies.
- The creation and coordination of networks of existing genomic projects in subjects relevant to genetic diversity and the use of genetic resources, incorporating wild species and relatives of crop plants.

- Functional genomics, including proteomics and metabolomics, resulting in the development of EST-based markers.
- The full exploitation and understanding of the concept of association genetics (linkage disequilibrium) to discover useful genes in germplasm.
- Development of allele-mining strategies.
- Application of comparative genetics and genomics to species that are less advanced in research knowledge.

Information: a key to utilization

Important components of existing and future research programs that look at genetic diversity are information collection, dissemination, and documentation. The raw material in germplasm collections cannot be used effectively without information on agronomic practices and the genetic traits of value to users including the harvested produce for food preparation and/or other uses. This information is obtained from farmers during the collecting of the germplasm material as well as through characterization and evaluation of the genetic material, increasingly using molecular methods. The free exchange of information, like the flow of germplasm, can be impeded or facilitated by policies and legal instruments, and that provision of information on genebank holdings by information networks in the public domain, such as SINGER (http://www.singer.cgiar.org), are crucial to optimal management and use of the collections of agricultural and forestry biodiversity.

Efforts must be made at international levels to design integrative databases that include passport, morphological, field, pedigree, molecular, and sequencing data. Development of species-specific marker databases and ontologies will provide breeders and researchers with valuable tools for understanding genetic diversity. In addition, databases that bring together ethnobotanical and indigenous knowledge information and nutritional data will advance our understanding of the use of agricultural biodiversity.

Diversity and ecosystems

Agricultural biodiversity contributes not only to improved production and increased productivity, it also makes substantial contributions to ecosystem services in agroecosystems and can be used to improve the health of other ecosystems. However, the nature of the contribution and the critical elements that depend on diversity per se are not well understood. Knowledge is particularly limited in areas such as economics and diversity analysis, the nature and distribution of below ground diversity, and the interaction of on-farm diversity with that in wider ecosystems. There are also other areas to be investigated, including the benefits of using crop diversity in production systems as a form of integrated pest management and the integrated management of soil nutrients.

In agricultural production systems, crop and agroforestry diversity help support such ecosystem services as watershed management, carbon sequestration, and regulation of greenhouse gases, nutrient cycling, biological control of pests and diseases, soil stabilization and the regulation of soil physical and chemical properties. However, the nature of these relationships is poorly understood and the factors critical for optimum function still need to be determined. Investigating the relationships between diversity and functional efficiency for these key ecosystem services should be carried out in selected production systems and at different scales. This will result in models that will enable prediction of the impacts of diversity change on key functions and ecosystem services.

Increased use of agricultural biodiversity has the potential for substantial positive contributions to other ecosystems. Approaches that reduce the use of synthetic chemical inputs (herbicides, pesticides, and fertilizers) often involve increased use of crop, livestock, and other diversity (for example, in the case of new materials incorporating increased pest and disease resistance). Benefits can also be expected from improvements in agricultural biodiversity management that reduce wild harvesting (for example, for fuel wood or of medicinal plants). The "natural" elements of production systems and nearby areas are often an integral part of traditional production practices. Traditional knowledge thus furnishes important information on when to sow and undertake other cultural practices based on bird migration, flowering periods, animal mating periods, and so on. A more integrated approach exploring the ways in which natural and productive components interact is likely to strengthen sustainability of production.

Diversity and economics

Our understanding and appreciation of the economic value of agricultural biodiversity remains limited. A framework for estimating the economic value of biodiversity has begun to be developed and a number of studies have examined the value of crop diversity maintained in *ex situ* collections and in production (Swanson 1996; Smale *et al.*, 2003). However, these have yet to be extended to a wider appreciation of agricultural biodiversity *in toto*. The biodiversity maintained by farmers is not only of benefit to them but also to society as a whole because of its role in maintaining ecosystem services. The benefits for farmers of retaining biodiversity are demonstrable but not yet adequately quantified, and will only be fully realized and rewarded when other sectors of society accept and pay full value for them, either directly as part of the price of produce or indirectly through taxes. Equitable cost sharing across different sectors of society will increase the rate of adoption of improved biodiversity management practices by farmers. Such approaches have important policy implications that also need to be explored.

Diversity and farmers

The maintenance and use of crop diversity (and other diversity) in production systems ultimately depends on its value to farmers. Farmers are therefore central to any work aimed at improving our maintenance and use of agricultural biodiversity, and are increasingly directly engaged in the research work undertaken. For crop diversity substantial evidence is now accumulating on the way in which maintenance of high levels, based largely on traditional cultivars, meets the needs of resource-poor farmers. These include (Jarvis *et al.*, 2004):

- Risk avoidance or management, for example, in respect of climatic uncertainties or pest and disease problems.
- Food security in respect of total food supplies and nutritional well being.
- Multiple uses for food, forage, construction materials, brewing.
- Income generation providing products that can be sold in different markets or are of high value.
- Meeting cultural or religious needs through providing specific products for special ceremonies.
- Optimizing land use to ensure cultivars are available for difficult (stony, wet, cold) lands.
- Adaptation to changing conditions such as increasing drought.

It has often been noted that traditional cultivars can play a particularly important role in rural communities following major environmental disasters, civil disturbance, or wars. In these situations, disruption and limitations of resource availability often increases the importance of local crop materials (Sperling and Longley, 2002). At the same time food aid and seed aid can materially disrupt traditional production patterns and local seed systems and place local resources at risk (Richards and Ruivenkamp, 1997)

Working with farmers, IPGRI and other organizations are identifying a number of ways in which maintenance of diversity to meet these needs can be supported. Examples include (Jarvis *et al.*, 2004):

- Creating methodologies for integrating locally adapted crop cultivars and farmer preferences into national and local development and extension projects.
- Improving access of materials to farmers through developing seed networks, diversity fairs, and information systems.
- Market development for the maintenance of on-farm diversity, including better processing, marketing, and consumer awareness.
- Providing information on nutritional qualities of locally adapted cultivars that can provide low-cost forms of improved nutrition.
- Developing participatory breeding and selection programs to overcome key constraints.

Supporting these specific actions there will need to be an improved understanding of farmer and community institutions and of the ways in which they can be strengthened and rural communities empowered. Local organizations, farmer groups, and nongovernmental organizations (NGOs) will be increasingly important in this regard, and partnerships between formal and informal institutions will be crucial. This is likely to include innovative partnerships with the private sector, for example to design green labeling experiments that benefit farmers directly and mainstream biodiversity management practices as part of codes of conduct used by some large food distribution companies. Key actions that have been proposed to strengthen the value of traditional and/or niche varieties include:

- Determining market and nonmarket values to farm communities of diversity in selected sites.
- Determining the effect of market and nonmarket variables on diversity (for example, local and international prices, land tenure, population pressure, grazing and cropping intensity).
- Determining ways of using diversity to address key production constraints (biotic and abiotic stress) and livelihood needs (nutrition and health).
- Exploring how the process of selection by local communities for improved agrobiodiversity components (crops, livestock, fish) affects the interactions and synergies of the agroecosystem and the valuation of the diversity to the rural poor.

Future Challenges

The challenge is to develop the knowledge needed to maintain and use agricultural biodiversity from a holistic or systems perspective. Biodiversity management is knowledge intensive. Agricultural biodiversity research has typically focused on specific components–crops, pests, livestock–whereas farmers manage the whole system as well as its individual components using a rich basis of traditional knowledge. Realizing the benefits of biodiversity for both agricultural production and ecosystem services requires management at the plot and farm level and well beyond. A major scientific contribution will be to utilize integrated natural resources management approaches to develop biodiversity management support tools at the farm and landscape scales.

The conservation and sustainable use of agricultural biodiversity is not an end in itself, but a means of improving the lives of people and ensuring their future well-being. The emphasis in agricultural biodiversity research is thus invariably on useful biological organisms. The challenge of IPGRI's agenda, and those of other organizations working in the area, is to try to identify approaches that together contribute to making agriculture more productive, peoples' lives more secure and healthy, and ecosystems on which agriculture is based protected and improved. To accomplish all of these aims without compromising any of them will mean intensified efforts to link research with development.

One way of achieving this linkage is to emphasize the value of conserving diversity through its continued use. Important elements in this approach include the determination of economic and other values of diversity, the promotion of neglected and underutilized crops and indigenous species (Padulosi *et al.*, 2002), the identification and promotion of policies or incentives for improved maintenance and use of diversity, the development of international commodity chains for crops, the increased use of diversity in pre-breeding and breeding and support to base broadening efforts (Cooper *et al.*, 2001). It will also involve the management of biodiversity in production systems that will be directed at environmental maintenance, reducing production costs, and developing more sustainable ways of farming and managing germplasm collections.

The need to develop a stronger research effort on agricultural biodiversity is now widely accepted, and a number of international initiatives have been undertaken to support the identification of the key questions and to bring researchers together around a common agenda. International meetings have been held sponsored by FAO, the CBD Secretariat and the Netherlands in 1998, the United Nations University, IPGRI and the CBD Secretariat in 2001, and the Systemwide Programme on Genetic Resources (SGRP) of the CGIAR in 2003. These have identified key characteristics needed for the research (for example, use of participatory approaches, building on traditional knowledge, adopting an ecosystem approach, multidisciplinarity) and identified some key topics where work is urgently needed, including:

- Methods for measuring diversity.
- Understanding linkages, associations, and interactions.
- Investigating links to resilience, stability and productivity.
- Ensuring the maintenance of adaptability and ecosystem function.
- Economic analyses of ecosystem function.
- Determining how to combine intensification with diversity maintenance.
- Strengthening biodiversity content in the development and adoption of new practices.

In all these endeavors it is essential to remember that diversity continues to be maintained and managed by farmers throughout the world as an integral part of their production strategies. Their biological resources (crop, livestock, and other diversity) are often one of their key livelihood assets. Knowledge gained and practices developed need to reflect this and integrate new practices within a framework that strengthens farmer management and use of their resources.

One suggestion that was put forward at the 2003 SGRP Nairobi workshop on agricultural biodiversity was to establish a “facilitation unit” to support the work of the research community and its partners. This unit would:

- Act as the focal point for any agricultural biodiversity research group.
- Try to build a repository of relevant knowledge and of access to relevant information.

- Catalyze the creation of an inventory of work and expertise.
- Stimulate the development of communities of practice in relevant areas.
- Promote action research.
- Support the development of linkages around common research issues.
- Share ideas for project proposals and funding information.
- Liaise with established groups such as the CBD Secretariat and FAO.

The benefits would include an opportunity to raise awareness on what is being done on agricultural biodiversity, a clearer identification of linkages between components of agricultural biodiversity and strengthened capacity among partners to incorporate agricultural biodiversity components in their work and to manage work in ways that reflect agricultural biodiversity needs. It would also provide opportunities for increased exchange of information, collaboration on resource mobilization, and support for the development of joint projects. The idea of a facilitation unit of this type was endorsed by COP VII of the CBD at its 2004 meeting.

Conclusion

Ways must be found to ensure an increase in agricultural productivity in order to keep pace with the rise of the world population and the growing demand for good quality food. This increase must occur, and be sustained, in the face of climate change, diminishing land availability, and global conflict. The challenges are global in nature; the strategies to be developed and the tools made available to meet these challenges must also be global in nature. Agricultural biodiversity, and specifically crop genetic resources, are the result of millennia of agricultural activity by farmers from every region of the world, and qualify as global public goods that require global efforts to ensure that all countries have fair access and equitable share in benefits. However, we lack the basis of knowledge required to use this diversity optimally, to ensure that its maintenance and use fully benefit farmers and communities and to mobilize it to best meet the food needs of the future.

References

Bajracharya, J., B.K. Baniya, B. Sthapit, and J.Witcombe. 2004. The genetic diversity of traditional rice varieties in Nepal. Crop Science (submitted).

CGIAR. 2003. Research for Sustainable Development: From Words to Action. Annual Report 2002. Consultative Group on International Agricultural Research.

Cooper, D., C. Spillane, and T. Hodgkin. 2001. Broadening the genetic base of crop production. CABI, Wallingford, UK, 452 p.

Doebley, J. 1990. Molecular evidence and the evolution of maize. Economic Botany, 44, supplement, 6-27.

FAO. 1998. The state of the world's plant genetic resources for food and agriculture. Food and Agriculture Organization of the United Nations, Rome,510 p.

FAO. 2002. Review and development of indicators for genetic diversity, genetic erosion and genetic vulnerability (GDEV): Summary report of a joint FAO/IPGRI workshop, Rome, 11-14 September 2002, Rome, Italy.

Guarino, L., A. Jarvis, R.J. Hijmans, and N. Maxted. 2001. Geographic information systems and the conservation and use of plant genetic resources. In: J.M.M. Engels, V. Ramanatha Rao, A.H.D. Brown, and M.T.Jackson (eds.). Managing Plant Genetic Diversity, CABI Publishing, Wallingford, UK, p. 387-404.

Hanotte, O., D.G. Bradley, J.W. Ochieng, Y. Verjee, E.W. Hill, and J.E.O. Rege. 2002. African pastoralism: genetic imprints of origins and migrations. Science, 296, 336-339.

Imperial College, Wye. 2003. Crop diversity at risk: the case for sustaining crop collections. The Department of Agricultural Sciences, Imperial College Wye, UK, 31p.

Jarvis, D.I., V. Zoes, D. Nares, and T. Hodgkin. 2004. On-Farm Management of Crop Genetic Diversity and the Convention on Biological Diversity's Programme of Work on Agricultural Biodiversity. Plant Genetic Resources Newsletter (in press).

Koo, B., and B. Wright. 2003. Strategies for timely evaluation of genebank accessions. In Biotechnology and genetic resource policies: Brief 10: What is a genebank worth? (ed. M. Smale and B.Koo) International Food Policy Research Institute, 3 p.

Louette, D., A. Charrier, and J. Berthaud. 1997. In situ conservation of maize in Mexico: genetic diversity and maize seed management in a traditional community. Economic Botany 51: 20-38.

National Research Council. 1972. Genetic Vulnerability of Major Crops, National Academy of Sciences, Washington, D.C.

Padulosi, S., T. Hodgkin, J.T. Williams, and N. Haq. 2002. Underutilized crops: trends, challenges and opportunities in the 21st Century. In "Managing plant genetic resources" Engels, J.M.M. et al .(eds), CABI-IPGRI. p.323-338.

Plucknett, D.L., N.J.H. Smith, J.T. Williams, and N.M. Anishetty. 1987. Genebanks and the World's Food. Princeton University Press, Princeton, 247 p.

Richards, P., and G. Ruivenkamp. 1997. Seeds and survival. IPGRI, Rome, Italy, 63 p.

Settle, W. 2001. Functional diversity in integrated crop management. In: Managing Biodiversity in Agricultural Ecosystems: An International Symposium. CD Available from UN University and at http://www.unu.edu/.

Smale, S., E. Meng, J.P. Brennan, and R. Hu. 2003. Determinants of spatial diversity in modern wheat: examples from Australia and China. Agricultural Economics, 28, 13-26.

Sperling, L., and C. Longley. 2002. Beyond Seeds and Tools: Effective Support to Farmers in Emergencies. Disasters, Vol. 26 Issue 4, p. 283, December.

Sthapit, B.R., K.D Joshi, and J.R. Witcombe. 1996. Farmer participatory crop improvement. III Participatory plant breeding, a case study for rice in Nepa., Experimental. Agriculture, 32:479-496.

Subedi, A., P. Chaudhary, B.K. Baniya, R.K. Tiwari, D.K. Rijal, and B.R. Sthapit. 2003. Who maintains crop genetic diversity and how: implications for on-farm conservation and utilization. Science and Culture (in press).

Swanson, T. 1996. Global values of biological diversity: the public interest in the conservation of plant genetic resources for agriculture. Plant Genetic Resources Newsletter, 105: 1-7.

Tahiri, A. 2004. Seed systems in Morocco. In: D. Jarvis, R. Sevilla, and T. Hodgkin (eds.) Seed systems and crop genetic diversity on farm. International Plant Genetic Resources Institute, Rome (in press).

Tanksley, S.D., and S.R. McCouch. 1997. Seed Banks and Molecular Maps Unlocking Genetic Potential from the Wild. Science, 277: 1063-1066.

Zimmerer, K.S., and D.S. Douches. 1991. Geographical approaches to crop conservation: the partitioning of genetic diversity in Andean potatoes. Economic Botany, 45: 176-189.

Chapter 17

Exploiting Biodiversity and Protecting the Environment

Klaus Ammann

Introduction

In agriculture, the rapid decline in species, varieties, and genetic diversity has been brought about by the success of new commercial varieties. There are reports of losses of over 80% of varieties in species such as apple, maize, tomato, wheat, and cabbage worldwide (UNEP World Conservation Monitoring Centre, 2003). Studies in population genetics raised concerns about genetic erosion. As well, the recognition of the importance of plant genetic material in the development of new varieties led to the establishment in the 1970s of the International Plant Genetic Resources Institute in Rome (FAO, 2003; IPGRI, 2003), and increased efforts to collect germplasm for *ex situ* collections.

The marked decrease in the number of butterfly species in Flanders (north Belgium) in the 20th century was illustrated by Maes and Van Dyck (2001), using data from a national butterfly mapping scheme. Nineteen of the 64 indigenous species have become extinct, and half of the remaining species are now threatened. Flanders has the highest number of extinct butterflies in Europe. More intensive agriculture practices and expansion of housing and road building increased the extinction rate more than eightfold in the second half of the 20th century.

Terrestrial and aquatic biodiversity within and around agricultural fields has been strongly influenced by agricultural practices (Tilman, 1999; Tilman *et al.*, 2002). Fertilizers, pest control chemicals, tillage, and even crop rotation have profoundly impacted the richness and diversity of agricultural ecosystems (Beringer, 2000; Ross *et al.*, 2002). Habitat fragmentation may have a more adverse effect in combination with disturbance.

Biotic stresses include weeds, insects, and plant pathogens such as fungi, viruses, and bacteria. Pesticides are commonly used to control these pests. Nevertheless, between 35 and 42% of the world's food and fiber is lost to pests despite the use of 2.5 million metric tonnes of pesticides (Oerke, 1994; Oerke and Dehne, 1997; Pimentel, 2001). Weeds cause 10-13% loss, insects 13-16%, and

pathogens 12-13%. Without pesticides or other control measures, the losses could increase to 70%, with an economic loss of US$400 billion yearly (Oerke and Dehne, 1997). Pest control measures are a positive economic investment for farmers yielding a return of US$3-4 for each dollar invested (Pimentel and Lehman, 1993).

Weeds are a major problem in many crops, so herbicides are required for control. Over 90% of US soybean hectarage and 70% of Brazilian and Argentine soybean hectarage are treated with herbicides (Oerke and Dehne, 1997). For maize, over 95% of US hectarage is treated with herbicides (USDA-NASS, 2002). Herbicide-tolerant crops can provide an opportunity to reduce herbicides in such systems. In the US, an average 10% reduction in herbicide usage was seen with herbicide-tolerant soy from 1995 to 1998 (Hin *et al.,* 2001). A more recent study showed a reduction of 13.04 million kg of active ingredient in herbicide-tolerant soya in the US in 2001 (Carpenter, 2001). In the EU, a standard maize herbicide program uses approximately 1740 g of active ingredient per hectare, but this amount could be reduced by 30-60% if genetically modified (GM) crop technology were adopted (Phipps and Park, 2002). Similar levels of herbicide reductions were projected for winter oilseed rape (for the UK) and sugar beet (for Denmark) of GM crops with herbicide tolerance were adopted in these countries (Phipps and Park, 2002). However, the most important contribution to a more sustainable practice is the shift from more toxic herbicides to glyphosate (Carpenter *et al.,* 2002)

Control of other pests is critical in a number of crops. High levels of insecticide are used to control ravaging insects in many of the world's cotton-growing areas, for example, reducing crop losses in some regions from 35–39 to 13% or less (Oerke, 2002; James 2002). Adoption of insect-protected cotton has impacted the level of insecticides used on this crop in many areas (James, 2002). In the US, the estimated savings of active ingredient are 848 tonnes in 2001 (Gianessi *et al.,* 2002), 1224 tonnes in 1999, and 907 tonnes in 1998 (Carpenter, 2001). In China, an 80% reduction in kilograms of formulated product used was due to the adoption of GM cotton (Huang *et al.,* 2003). Introducing GM cotton in Spain would lead to a 60% reduction in volume of pesticide used, and nearly a 40% reduction in active ingredient used (Phipps and Park, 2002). Similar reductions in pesticide use have occurred in Australia after the introduction of GM cotton (see Peacock, this volume).

Adverse Effects of Pesticide Use

Adverse effects of pesticide use in agriculture are well documented (Pimentel and Lehman, 1993). Conventional insecticides generally reduce diversity through direct toxic effects. Many of the widely used classes of conventional insecticides, including organophosphates and pyrethroids, adversely affect a broad range of nontarget species, including species of economic importance. Local extinctions are common where these insecticides are frequently used. Such insecticides eliminate important predator and parasitoid species from agricultural systems. (Pimentel *et al.,* 1993).

These impacts on natural enemies have been shown to lead to flare-ups in secondary pest species, some of which were not previously economically important. In a few cases, insecticides directly stimulate the population growth of nontarget pest species (for example, pyrethroids have such an effect on some mite and aphid species). In addition, the toxic effects of insecticides can lead to food chain effects because of decreased food availability for higher trophic levels, and bioaccumulation of the insecticides. For example, organ chlorine use and ingestion by earthworms has led to die-offs of birds feeding on these species. Replacing broad-spectrum insecticides with more specific, softer alternatives is necessary to avoid these impacts.

Some herbicides also can be toxic to invertebrates. However, the more important effects of herbicide use with respect to biodiversity are to reduce noncrop plant (weed) populations and weed seed production in agricultural fields. Where herbicide use is intensive, adverse impacts may be seen on various vertebrate and invertebrate species that depend upon these plant (weed) species for food or shelter. Where invertebrate populations are strongly affected, consequences for higher trophic levels also may occur.

Benbrook's (2003) claim of increased pesticide use due to the advent of genetically modified crops does not hold up to close scrutiny. According to Parrott (2004), Benbrook's assumptions are not necessarily valid, and he ignores the fact that amount of active ingredient and environmental impact are not the same thing. While there are definitely cases where the amount of active ingredient use has increased, overall environmental impact has decreased (Fernandez-Cornejo and McBride, 2002; their section on Adoption and Pesticide Use is the most relevant to the topic).

Tillage and Fertilizer Use

The impact of tillage on biodiversity in agricultural fields includes the disruption of in-field communities and reduction of soil quality. The impact of tillage on natural habitats is even greater. Soil erosion due to tillage leads to high levels of fertilizers and pesticides being carried off agricultural fields into waterways. The past 35 years have seen a 6.87-fold increase in nitrogen fertilization and a 3.48-fold increase in phosphorus fertilization within intensive agricultural systems (Tilman, 1999; Tilman *et al.*, 2002). As they move into aquatic systems, these chemicals can have direct toxic effects on natural communities, and the fertilizers cause eutrophication. Eutrophication leads, in turn, to direct losses in biodiversity, pest outbreaks, and changes in the structure of natural communities. In addition, because erosion leads to various forms of nitrogen and fertilizer dust being redistributed aerially, natural terrestrial ecosystems are also undergoing eutrophication (Hayati and Proctor, 1991; Woo and Zedler, 2002). Many of these problems can be reduced or avoided by reducing tillage practices. In North America and Europe, high-yield farming and conservation tillage have reduced soil erosion by 65-98% (Buffett, 1996). However, subsistence farming in developing countries is causing substantial soil erosion and habitat loss, and is a significant threat to natural biodiversity.

Genetically Modified Crops and Natural Biodiversity

GM crops have the ability to benefit natural biodiversity in a number of ways. First, GM crops have the demonstrated potential to increase yields and decrease variability in yields (Gianessi *et al.*, 2002), thereby reducing the need to put additional land into agricultural production. By slowing the rate at which natural habitats are destroyed, GM crops and other technologies that increase agricultural productivity can help to preserve natural biodiversity. Second, insect-resistant crops reduce the use of broad-spectrum insecticides that would otherwise have direct and indirect effects on natural communities dwelling near agricultural fields. The insecticidal proteins expressed in Bt crops are highly specific and contained within the plant, minimizing the possibility of any off-site effects due to spray drift. Third, herbicide-tolerant crops facilitate a reduction in tillage, thereby reducing soil erosion, eutrophication, and contamination of aquatic communities.

Impacts of GM Crops on Genetic Diversity

Claims that herbicide-tolerant crops could eventually be harmful to the biodiversity of a whole landscape, including bird fauna, have been questioned. Johnson (2000) stated: "T*he irony is that biotechnology may hold the key to less damaging forms of agriculture, yet it appears that it is currently being used by some parts of the industry in some countries to produce the opposite effect. We are challenging the industry to change direction in R&D, toward producing crops that contribute to more sustainable forms of agriculture, demonstrating real and tangible benefits for the environment. I believe this needs to be done wherever the products of biotechnology are intended to be used, whether in industrial or developing countries.*"

Recent results (Elmegaard and Pedersen, 2001; Strandberg and Pedersen, 2002) reveal that the implementation of Roundup Ready® fodder beets may increase biodiversity in beet fields. In general, the weed flora and arthropod fauna in Roundup Ready plots contained more individuals and species than the tillage plots in June. These results cannot be generalized, and they may be different from crop to crop and from region to region. The results may heavily depend on the application mode and the kind of herbicide. Organic agriculture tends to enhance biodiversity in the field at the cost of yield, but energy input during the production process is also lower (Mäder *et al.*, 2002; Stokstad, 2002; Zoebl *et al.*, 2002; Goklany, 2002). Despite persisting scepticism about new agricultural strategies (organic or biotech), there is considerable potential to be realized in making food production still more ecologically based. It remains to be shown how widespread organic farming in large areas can effectively control pests. Still, the vision is justified to develop new GM crops, better adapted to the local ecological conditions. This would reduce fertilizer use, pesticide use, and enhance biodiversity directly through more crop diversity and indirectly through enhancing biodiversity in the field.

British Farm Scale Experiment 2003

This next section illustrates the present day debate about GM crops and their impact on biodiversity in the U.K. Highly publicized even before it started, the experiment on herbicide application management was a 3-year experiment on three genetically modified herbicide-tolerant (GMHT) crops, over more than 200 fields in Great Britain. The results had a great impact on the press and the public (Brooks *et al.*, 2003; Champion *et al.*, 2003; Firbank, 2003; Firbank *et al.*, 2003; Haughton *et al.*, 2003; Hawes *et al.*, 2003; Heard *et al.*, 2003a, b; Roy *et al.*, 2003; Squire *et al.*, 2003; Zeki, 2003; Freckleton *et al.*, 2003). The well intended experiments yielded considerable data related to herbicide and crop management differences–rigorously collected and duly peer reviewed.The results can be summarized as follows:

- Differences in biodiversity between crops exceed differences between GMHT and conventional crops (Brooks *et al.*, 2003; Haughton *et al.*, 2003; Hawes *et al.*, 2003; Heard *et al.*, 2003a,b; Roy *et al.*, 2003).
- Higher early season weed numbers and biomass in all three GMHT crops (Heard *et al.*, 2003a,b).
- Higher weed mortality in GMHT sugar and canola resulting in lower late-season biomass and seed rain of weeds in those crops, but lower weed mortality in GM maize (Heard *et al.*, 2003).
- More detritivores (collembola) in all three GMHT crops as a result of higher weed detritus (Brooks *et al.*, 2003; Haughton *et al.*, 2003).
- Lower numbers of bees, butterflies, and Heteroptera in GMHT sugar beet and canola as a result of reduced weed populations; generally higher numbers of invertebrates in GM maize (Brooks *et al.*, 2003; Haughton *et al.*, 2003).
- Lower herbicide inputs in GMHT crops (Champion *et al.*, 2003).

It has been argued that GM maize is performing better, because it has been treated with the broadband herbicide atrazine; however, Perry *et al.*, (2003) showed with a more detailed analysis of data from the trials that this is not the case. Even GM maize treated with non-atrazine herbicides performed better than non-GM maize (see Figure 1 in Perry *et al.*, 2003). This explains why GM maize (the crop with best biodiversity performance in the trials) still performs better than the non-GM maize treated with non-atrazine herbicides. Benefits for biodiversity with herbicide-tolerant GM maize are obvious.

In the experiments, the GMHT crops were planted in Great Britain for the first time, and farmers actually have not been experienced enough to apply advanced techniques such as no tillage, which would have then given full advantage of the GMHT method.

It is quite logical, and has never been contested, that the application of a broadband herbicide such as Roundup Ready would be efficient in killing weeds, and as a consequence the biodiversity within the field is reduced with all its follow-ups, which have been studied in detail. The farm-scale studies actually could be summed

up in a simple message: no weeds ‡ no insects and ‡ no weed seed. In turn, no insects and no weed seed ‡ no bird food. No bird food ‡ no birds.

But it is not that simple: First of all, we have again to realize that we are not dealing with natural habitats, and even the skylark is an artificial product of agriculture, as much as we all love the song of these unique birds. If that is so, then we will have the chance to manage better, since we are dealing with highly dynamic ecosystems. With only little change we will be able to get more biodiversity back in the fields by applying appropriate methods. The U.K. farm scale experiments fail to take into account that management methods have changed in the US with the advent of GM crops. It is not appropriate to compare in a seemingly scientific way two so different systems in fields divided in half. Experimental outlays in field research need to take into account the full potential of management in modern farming such as no tillage. Even if seen as a true management experiment, it is not done in a true farm scale manner: it fails to compare yield and other input-output data, to residue analysis of conventional herbicides within the non-GM crop fields. It would have been possible to apply standard methods used in integrated pesticide management systems such as the Cornell Environmental Impact Formula (Levitan *et al.*, 1995; Levitan, 2000; Kovach *et al.*, 2003).

Squire *et al.*, (2003) stated: "When, in the USA, large areas of crops were replaced by GMHT varieties, the profile of agrochemical inputs on the farm changed, the proportion of the land that was tilled before sowing sometimes decreased, less chemicals were lost in leachates and run-off from the field, and, as glyphosate and glufosinate ammonium are relatively short lived and of low toxicity to animals, the change in profile was considered to lessen the wider impact of farming (Carpenter *et al.*, 2002; Phipps and Park, 2002). The chain of impacts was not the same for all crop species, and generalizations are difficult (Carpenter *et al.*, 2002; Fernandez-Cornejo and McBride, 2002)."

If all those data had been available and a better adapted management had been applied, results would not look so bleak for the Roundup Ready technology. This has been shown for economic data in Romania. Economically it is indeed rewarding to use the Roundup Ready technology there (Brookes, 2003). Overall, with the flexibility and simplicity of the herbicide-tolerant crop method, it will be easier to make progress where the farmers do not like too much weed component in the harvest, because there are a number of problematic toxicity cases connected to certain weed species (Damron, 1998; Damron and Jacob, 2003).

With the economic incentive, farmers will agree more readily to do something extra for agricultural biodiversity to enhance conservation in arable fields (see the chapters on no-tillage and pesticide sections: Mineau and McLaughlin, 1996; Nentwig, 1999). It will be rewarding to see the data of the U.K. Farm Scale experiments explored by more researchers–a laudable move by the farm-scale research coordinators–especially if statisticians have a closer look at variation, dynamics, and individual treatments. Some of those treatments could well reveal key data on how to enhance successfully biodiversity in the field with GMHT crops. In

the first round, researchers concentrated on the big question of comparing the two technologies as a whole, and also with sound statistics of average values that could have been achieved with less "statistical overkill," and that bury the subtle details from which we could learn more. Having a closer look at variation related to the individual management methods would most probably also have the potential of projection into future strategies. As a whole, we encounter the same phenomenon often seen in scientific controversies on complex ecological issues: It is easy to lose sight and to pick out in a reductionist manner data that fit your own view. It is more difficult to keep an open mind and to analyze agricultural issues on biotechnology and biodiversity within a truly holistic approach. Chassy *et al.*, (2003) comment that the really important questions have not yet been asked.

Conclusion

The greatest threat to natural biodiversity comes from habitat loss, much of which is driven by agricultural demand. Increasing the productivity of land currently in production is necessary to slow this process. Other agricultural practices also can negatively impact natural communities through various off-site effects, including movement of fertilizers into aquatic systems and pesticidal drift. Reducing tillage and decreasing the use of pesticides can mitigate some of these impacts. GM crops can be a partial solution to several of these problems. GM crops enhance productivity, minimize off-site effects, and (in the case of herbicide-tolerant crops) facilitate reductions in tillage. GM crops can fit well with other farming practices as long as the specific usage prescribed is not neglected. Also, GM crops can theoretically be included within organic and integrated farming strategies, and they might help to develop new knowledge-based agricultural practices in the future.

References

Andow, D.A. 2003. UK farm-scale evaluations of transgenic herbicide-tolerant crops. Nature Biotechnology 21: 1453-1454.

Benbrook, C. 2003. Impacts of Genetically Engineered Crops on Pesticide Use in the United States: The First Eight Years. C Benbrook, ed, Vol. 2004.

Beringer, J.E. 2000. Releasing genetically modified organisms: will any harm outweigh any advantage? Journal of Applied Ecology, 37: 207-214.

Brookes, G. 2003. The farm level impact of using Roundup Ready soybeans in Romania. Vol. 2003. Graham Brookes, Canterbury, Kent, UK.

Brooks, D., D. Bohan, G. Champion, A. Haughton, C. Hawes, M. Heard, S. Clark, A. Dewar, L. Firbank, J. Perry, P. Rothery, R. Scott, I. Woiwod, C. Birchall, M. Skellern, J. Walker, P. Baker, D. Bell, E. Browne, A. Dewar, C. Fairfax, L. Garner, B. Haylock, S. Horne, S. Hulmes, N. Mason, L. Norton, P. Nuttall, Z. Randle, M. Rossall, R. Sands, E. Singer, and M. Walker. 2003. Invertebrate responses to the management of genetically modified herbicide tolerant and conventional spring crops. I. Soil-surface-active invertebrates. Phil. Trans. R. Soc. Lond. B 358: 1847–1862.

Buffett, H. 1996. The partnership of biodiversity and high yield agricultural production. Diversity 12: 16-17.

Carpenter, J., A. Felsot, T. Goode, M. Hammig, D. Onstad, and S. Sankula. 2002. Comparative Environmental Impacts of Biotechnology-derived and Traditional Soybean, Corn, and Cotton Crops. Council for Agricultural Science and Technology, CAST, Ames, Iowa.

Carpenter, J.E. 2001. Case study in benefits and risks of agricultural biotechnology: roundup ready soybeans and Bt corn. In. National Center for Food and Agricultural Policy.

Champion, G., M. May, S. Bennett, D. Brooks, S. Clark, R. Daniels, L. Firbank, A. Haughton, C. Hawes, M. Heard, J. Perry, Z. Randle, J. Rossall, P. Rothery, M. Skellern, R. Scott, G. Squire, and M. Thomas. 2003. Crop management and agronomic context of the Farm Scale Evaluations of genetically modified herbicide-tolerant crops. Phil. Trans. R. Soc. Lond. B 358: 1801-1818.

Chassy, B., C. Carter, M. McGloughlin, A. McHughen, W. Parrott, C. Preston, R. Roush, A. Shelton, and S.H. Strauss. 2003. UK field-scale evaluations answer wrong questions. Nature Biotechnology 21: 1429-1430.

Damron, B.L., and J. Jacob. 2003. Toxicity to Poultry of Common Weed Seeds. In EDIS. This document is Fact Sheet PS-55, one of a series of the Animal Sciences Department, Florida Cooperative Extension Service, Institute of Food and Agricultural Sciences, University of Florida. First published February 2001. EDIS web site at http://edis.ifas.ufl.edu. Vol 2003. University of Florida Extention Services.

Damron, B.L. 1998. Toxicity of weed seeds common to the Southeastern United States: A review. Journal of Applied Poultry Research 7: 104-110.

Elmegaard, N., and M.B. Pedersen. 2001. Flora and Fauna in Roundup Tolerant Fodder Beet Fields. NERI Technical Report, No. 349.

FAO. 2003. Biodiversity in Food and Agriculture. How does Biodiversity benefit natural and agricultural ecosystems? Vol. 2003. FAO

Fernandez-Cornejo, J, and W. McBride. 2002. Adoption of Bioengineered Crops. ERS Agricultural Economic Report No. AER810. 67 p, May.

Firbank, L. 2003. Introduction to the Farm Scale Evaluations of spring-sown genetically modified crops. Phil. Trans. R. Soc. Lond. B 358: 1777-1778.

Firbank, L.G., M.S. Heard, I.P. Woiwod, C. Hawes, A.J. Haughton, G.T. Champion, R.J. Scott, M.O. Hill, A.M. Dewar, G.R. Squire, M.J. May, D.R. Brooks, D.A. Bohan, R.E. Daniels, J.L. Osborne, D.B. Roy, H.I.J. Black, P. Rothery, and J.N. Perry. 2003. An introduction to the Farm-Scale Evaluations of genetically modified herbicide-tolerant crops. Journal of Applied Ecology 40: 2-16.

Freckleton, R., W. Sutherland, and A. Watkinson. 2003. Deciding the Future of GM Crops in Europe. Science 302: 994-996.

Gianessi L.C.S., S. Sankula, and J. Carpenter. 2002. Plant Biotechnology: Current and Potential Impact for Improving Pest Management in US Agriculture, An Analysis of 40 Case Studies. Vol. 2003.

Goklany, I.M. 2002. The ins and outs of organic farming. Science 298: 1889.

Haughton, A., G. Champion, C. Hawes, M. Heard, D. Brooks, D. Bohan, S. Clark, A. Dewar, L. Firbank, J. Osborne, J. Perry, P. Rothery, D. Roy, R. Scott, I. Woiwod, C. Birchall, M. Skellern, J. Walker, P. Baker, E. Browne, A. Dewar, B. Garner, L Haylock, S. Horne, N. Mason, R. Sands, and M. Walker. 2003. Invertebrate responses to the management of genetically modified herbicide-tolerant and conventional spring crops. II. Within-field epigeal and aerial arthropods. Phil. Trans. R. Soc. Lond. B 358: 1863–1877.

Hawes C., A. Haughton, J. Osborne, D. Roy, S. Clark, J. Perry, P. Rothery, D. Bohan, D. Brooks, G. Champion, A. Dewar, M. Heard, I. Woiwod, R. Daniels, M. Young, A. Parish, R.L.G.F. Scott, and G. Squire. 2003. Responses of plants and invertebrate trophic groups to contrasting herbicide regimes in the Farm Scale Evaluations of genetically modified herbicide-tolerant crops. Phil. Trans. R. Soc. Lond. B 358: 1899–1913.

Hayati, A.A., and M.C.F Proctor. 1991. Limiting nutrients in acid mire vegetation: peat and plant analyses and experiments on plant responses to added nutrients. J. Ecol. 79: 75-95.

Heard, M., C. Hawes, G. Champion, S. Clark, L. Firbank, A. Haughton, A. Parish, J. Perry, P. Rothery, D. Roy, J. Scott, M. Skellern, G. Squire, and M. Hill. 2003a. Weeds in fields with contrasting conventional and genetically modified herbicide-tolerant crops. II. Effects on individual species. Phil. Trans. R. Soc. Lond.

Heard, M., C. Hawes, G. Champion, S. Clark, L. Firbank, A. Haughton, A. Parish, J. Perry, P. Rothery, J. Scott, M. Skellern, G. Squire, and M. Hill. 2003b. Weeds in fields with contrasting conventional and genetically modified herbicide-tolerant crops. I. Effects on abundance and diversity. Phil. Trans. R. Soc. Lond. B 358: 1819-1832.

Hin, C.J.A., P. Schenkelaars, and G.A. Pak. 2001. Agronomic and environmental impacts of commercial cultivation of glyphosate tolerant soybean in the USA. Dutch Centre for Agriculture and Environment, Utrecht.

Huang, J., R. Hu, C.C.E.P. Fan, , and S. Rozelle. 2003. Bt cotton benefits, costs, and impacts in China. edition 5,4, Vol. 2003. AgBioForum, 153-166.

IPGRI. 2003. IPGRI, International Plant Genetic Resources Institute. Vol. 2003. Consultative Group on International Agricultural Research (CGIAR).

James, C. 2002. Preview No. 27: Global Status of Commercialized Transgenic Crops 2002. ISAAA Briefs No. 27. International Service for the Acquisition of Agri-Biotechnologies, Ithaca, N.Y.

Johnson, B. 2000. Genetically modified crops and other organisms: implications for agricultural sustainability and biodiversity. Gabrielle J. Persley, ed, Agricultural Biotechnology and the Poor. Consultative Group on International Agricultural Research, p 131-138, Washington, D.C.

Kovach, J., C. Petzoldt, J. Degni, and J. Tette. 2003. A Method to Measure the Environmental Impact of Pesticides. Vol 2003. Cornell University, Integrated Pest Management Program, Online Publications.

Levitan, L. 2000. “How to” and “why”: assessing the enviro-social impacts of pesticides. Crop Protection 19: 629-636.

Levitan, L., I. Merwin, and J. Kovach. 1995. Assessing the relative environmental impacts of agricultural pesticides: The quest for a holistic method. Agriculture Ecosystems & Environment 55: 153-168.

Mäder, P., A. Fliessbach, D. Dubois, L. Gunst, P. Fried, and U. Niggli. 2002. Soil Fertility and Biodiversity in Organic Farming. Science 296: 1694-1697.

Maes, D., and H. Van Dyck. 2001. Butterfly diversity loss in Flanders (north Belgium): Europe's worst case scenario? Biological Conservation 99: 263-276.

Mineau, P., and A. McLaughlin. 1996. Conservation of biodiversity within Canadian agricultural landscapes: Integrating habitat for wildlife. Journal of Agricultural & Environmental Ethics 9: 93-113.

Nentwig, W. 1999. Weedy plant species and their beneficial arthropods: potential for manipulation in field crops. University of California Press, Berkeley, Los Angeles, London.

Oerke, E.C. 1994. Estimated crop losses due to pathogens, animal pests, and weeds. In E.C. Oerke, H.W. Dehne, W.F. Schonbeck, Ae. Weber, (eds), Crop Production and Crop Protection. Elsevier Science Publishing, New York, N.Y., p 535-597.

Oerke, E.C. 2002. Crop losses due to pests in major crops. CAB International Crop Protection Compendium 2002. Economic Impact. CAB International, Wallingford, UK.

Oerke, E.C., and H.W. Dehne. 1997. Global crop production and the efficacy of crop protection - Current situation and future trends. European Journal of Plant Pathology 103: 203-215.

Parrott, W. 2004. Rebuttal of Technical Report No. 6 of C.M. Benbrook on the Pesticide Use 2004, personal communication: http://www.botanischergarten.ch/Maize/Parrott-Benbrook.pdf

Perry, J.N., P. Rothery, S.J. Clark, M.S. Heard, and C. Hawes. 2003. Design, analysis and statistical power of the Farm-Scale Evaluations of genetically modified herbicide-tolerant crops. Journal of Applied Ecology 40: 17-31.

Phipps, R.H., and J.R. Park. 2002. Environmental benefits of genetically modified crops: Global and European perspectives on their ability to reduce pesticide use. Journal of Animal and Feed Sciences 11: 1-18.

Pimentel, D. 2001. Pricing biodiversity and ecosystem services. Bioscience 51: 270-271.

Pimentel, D., and H. Lehman 1993. The Pesticide Question: Environment, Economics and Ethics. Chapman and Hall, New York.

Pimentel, D., L. McLaughlin, A. Zepp, B. Lakitan, T. Kraus, P. Kleinman, F. Vancini, W.J. Roach, E. Graap, W.S. Keeton, and G. Selig. 1993. Environmental and Economic-Effects of Reducing Pesticide Use in Agriculture (Reprinted from Biosci, Vol 41, p. 402, 1991). Agriculture Ecosystems & Environment 46: 273-288.

Ross, K.A., B.J. Fox, and M.D. Fox. 2002. Changes to plant species richness in forest fragments: fragment age, disturbance and fire history may be as important as area. J. Biogeography 29: 749-765.

Roy, D., D. Bohan, A. Haughton, M. Hill, J. Osborne, S. Clark, J. Perry, P. Rothery, R. Scott, D. Brooks, G. Champion, C. Hawes, M. Heard, and L. Firbank. 2003. Invertebrates and vegetation of field margins adjacent to crops subject to contrasting herbicide regimes in the Farm Scale Evaluations of genetically modified herbicide-tolerant crops. Phil. Trans. R. Soc. Lond. B 358: 1879–1898.

Squire, G., D. Brooks, D.A. Bohan, G. Champion, R. Daniels, A.J. Haughton, C. Hawes, M. Heard, M. Hill, M. May, J. Osborne, J. Perry, D. Roy, I. Woiwod, and L. Firbank. 2003. On the rationale and interpretation of the Farm Scale Evaluations of genetically modified herbicide-tolerant crops. Phil. Trans. R. Soc. Lond. B 358: 1779–1799.

Stokstad, E. 2002. Organic Farms Reap Many Benefits. Science 296: 1694-1697.

Strandberg, B., and M. Pedersen. 2002. Biodiversity in Glyphosate Tolerant Fodder Beet Fields. Timing of herbicide application. NERI Technical Reports, p. 36.

Tilman, D. 1999. Global environmental impacts of agricultural expansion: The need for sustainable and efficient practices. Proceedings of the National Academy of Sciences of the United States of America 96: 5995-6000.

Tilman, D., K.G. Cassman, P.A. Matson, R. Naylor, and S. Polasky. 2002. Agricultural sustainability and intensive production practices. Nature 418: 671-677.

UNEP World Conservation Monitoring Centre. 2003. Conservation Databases. Vol. 2003.

USDA-NASS. 2002. Census of Agriculture. Vol. 2003. U.S. Department of Agriculture, National Agricultural Statistics Service.

Woo, I., and J.B. Zedler. 2002. Can Nutrients Alone Shift A Sedge Meadow Towards Dominance By The Invasive Typha 3 Glauca? Wetlands 22: 509-521.

Zeki, S. 2003. Preface to: The Farm Scale Evaluations of spring-sown genetically modified crops. Phil. Trans. R. Soc. Lond. B 358: 1775–1776.

Zoebl, D., P. Maeder, A. Fliessbach, D. Dubois, L. Gunst, P. Fried, and U. Niggli. 2002. Organic Farming and Energy Efficiency. Science 298: 1890-1891.

Chapter 18

Preventing Agrobiodiversity Loss and Land Degradation in the Drylands of West Asia

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Introduction

The Rio de Janeiro Earth Summit (UNCED, 1992), followed 10 years later by the Johannesburg Sustainable Development Summit, confirmed the global challenge of the loss of biodiversity, desertification, and climate change. The international Convention on Biological Diversity (CBD), the UN Convention to Combat Desertification (UNCCD), and the UN Framework Convention on Climate Change (UNFCCC) signed by more than 150 countries or parties showed the willingness to minimize the effects and reverse the trends of these major environmental problems.

Land degradation and desertification effects are observed on one-third of Earth's land surface, affecting the livelihood of more than 2.6 billion people (Adams and Eswaran, 2000). The world loses more than 600 million hectares of land yearly due to desertification, and more than 100 countries are facing this environmental problem (El-Beltagy, 2002). Seventy-five percent of the arid and semi-arid lands including 83% of the rangelands and 60% of cropped lands are affected by desertification, not including the areas affected by soil and water salinization (Awni, 2002). The dry areas of West Asia and North Africa (WANA) are among the most threatened, with more than 90% of the land affected by desertification. Land degradation and desertification are accompanied by loss of vegetation cover, and most importantly the loss of rich biodiversity of these regions. The drylands of WANA encompass the major part of the Mediterranean biodiversity hot spot and the centers of origin, domestication, and diversity of many crops of global significance (Hawkes, 1983; Harlan, 1992). The trends of land degradation and loss of biodiversity will result in the loss of unique ecosystems, their valuable biodiversity, and environmental services, and consequently the disintegration of the prevailing livelihood systems causing further social problems of poverty and migration (World Bank, 2002).

The International Center for Agricultural Research in the Dry Areas (ICARDA) is working with national research systems to improve livelihoods and sustain the natural resources in the drylands of Central and West Asia, and North Africa. Within the GEF-UNDP funded project, ICARDA promotes the conservation and sustainable use of dryland agrobiodiversity in the Fertile Crescent center of diversity.

Importance of West Asia Dryland Agrobiodiversity

Drylands have been neglected by the world actions to preserve biodiversity, perhaps because they are areas with fewer species than tropical and equatorial regions. The value of biodiversity of the dry areas has been recognized recently because of its attributes as genetic resources that can withstand the major environmental constraints, and also for its importance in the life of migratory species. Dryland agrobiodiversity in particular has played a major role in food security and in sustaining agricultural development worldwide, and continues to provide the basis for the livelihood of local communities living under harsh environments. The West Asia region known as the "Fertile Crescent" is unique since it encompasses an area of megadiversity of important food crops and pasture species. It is one of the few centers where numerous species (notably wheat, barley, lentils, chickpea, pea, and vetch) originated 10,000 years ago. Seven genera of vascular plants are endemic to this region (Frankel, 1978; Harlan, 1992). These crops and species have spread to all parts of the world. The small grain crop species (wheat, barley, and food legumes) contribute 38% to our food worldwide.

Landraces of cereals, food legumes, and fruit trees, and their wild relatives found under natural habitats and still used by some farmers, constitute valuable germplasm. This germplasm can be used to breed for tolerance and resistance to major biotic and abiotic stresses, and for improving quality (ICARDA, 1997). However, this local plant diversity is continuously decreasing due to rapid degradation or loss of the natural habitats caused by the intensification and expansion of cultivation, overgrazing and overuse, and replacement of landraces by introduced species or the spread of newly released varieties. The loss of agrobiodiversity, accompanied by the degradation of other natural resources, will deprive the world of valuable genetic resources that can help reduce the effects of major global concerns due to desertification and global warming, and will increase the poverty of local communities. The fragility of the dryland ecosystems could lead to irreversible losses of land and biodiversity, making the restoration or rehabilitation efforts very costly or even impossible. Even the intensification practices and alternative land uses, often directly introduced to drylands, have shown their limitations in terms of sustaining the productivity and the natural resources. The conversion of rangelands and forests into cropping areas, and the excessive use of groundwater, have led to land degradation and depletion of fossil water and the abandonment of highly degraded areas. The encroachment of cereal and fruit tree cultivation continues to reduce

significantly the rangelands. It is estimated that 22% of the rangelands and 30% of forest areas will be reclaimed for agriculture purposes in the next 20 years in WANA, and there will be an increasing abandonment of cultivated lands due to urbanization, thereby decreasing productivity to uneconomic levels.

Eco-agriculture based on in situ conservation of local agrobiodiversity, and the integrated natural resources management and sustainable livelihoods strategies, are being promoted as the best approaches to allow for reconciliation between conservation of local agrobiodiversity and improvement of agricultural production. The focus should then be on the improvement of the livelihoods of the custodians of the agrobiodiversity, and on the increasing resilience of the prevailing ecosystems. All of the approaches advocated require the full involvement of the main stakeholders, principally farmers and herders individually or as communities and interest groups.

GEF-Dryland Agrobiodiversity Project

An holistic approach is taken in the project on conservation and sustainable use of dryland agrobiodiversity in Jordan, Lebanon, Palestine Authority, and Syria, funded by the Global Environment Facility (GEF) and the United Nations Development Programme (UNDP). It is coordinated at the regional level by ICARDA, which provides training and technical backstopping in cooperation with the International Plant Genetic Resources Institute (IPGRI) and the Arab Center for Studies in the Dry Areas and Arid Zones (ACSAD). The project is promoting the community-driven in situ conservation of landraces and wild relatives of 16 target genera, including wheat, barley, lentils, medics, lathyrus, vetch, Allium species, olive, almond, pear, plum, and pistachio. The project activities are conducted in two pilot target areas in each of the participating countries/authorities (Ajloun and Muwaqqar in Jordan, Baalbeck and Aarsal in Lebanon, Hebron and Jenin in the Palestinian Authority, and Al-Haffeh and Sweida in Syria). The main project outputs are:

- Better knowledge of status and trends of agrobiodiversity and its factors of degradation through ecogeographic surveys, farming systems and local knowledge surveys, and the use of GIS/RS tools.
- Demonstration of appropriate technological packages that can enhance the productivity of local agrobiodiversity.
- Promotion of added-value technologies and of alternative sources for the diversification of incomes of local communities.
- Reforms of existing policies and regulations to empower local communities and allow for sharing the benefits arising from the users of their conserved germplasm, as stated by most of the international conventions.
- Enhancing the capacity building of major stakeholders to work on sustainable agriculture and in situ conservation.

- Increasing public awareness at all levels.
- Strengthening of regional integration, coordination, and networking.

Site selection and implementation of project activities are done in close collaboration with local communities, NGOs, and local administrative authorities, as well as the national research and development institutions. Partnerships were created with other projects to increase synergies and harmonize the interventions and messages. Community-based actions are privileged and in the case of demonstrating technological packages, the farmers' school approach was adopted, using the lead farmers. Incentives are provided either through the government, resource mobilization or through the project to initiate and support partially a given community or individual farmer initiatives. The project has provided the training and the technical backstopping for women on areas of added-value technologies through processing of local products and on alternative sources of income opportunities. Links are developed with the private sector to improve the marketability of local products. This approach has been complemented by the participatory formulation of community development plans, natural habitats management plans, and sustainable livelihoods analysis as an exit strategy for further actions with targeted communities.

Major Factors of Degradation

The results of farming systems surveys showed the exclusive use of landraces in barley, lentils, and figs over all the sites, and the predominant use of olives, wheat, almond, and other fruit trees except apple and cherry in most of the sites. Though the hectarage of the small grain landraces is declining as they are replaced by the plantations of fruit trees (mainly cherry) as in Lebanon, olive or apple trees cover most of the target areas. Farmers have tested the newly released varieties of cereals and food legumes, which showed up to 30% grain yield gains, but quickly reverted back to landraces for grain quality and straw advantages. In the case of new varieties of grapes and olives, farmers are starting grafting the new varieties with the old landraces. The main threat for the landraces is the introduction of new species such as apple and cherry or the expansion of the olive tree plantations.

For the wild relatives and forage legumes found in forest areas, rangeland and on edges of field and roads, the major factors affecting their distribution and densities are overgrazing, the destruction of their natural habitats for reclaiming new lands for agriculture, and building purposes. These changes in land use are very often not submitted to long-term economic benefit analysis, and cases of failure of the alternative land uses have already been observed. In southern parts of Syria and in Jordan, there are many olive field orchards abandoned because of water scarcity problems. For apples, some farmers experienced heavy losses due to frost damage; and most of the farmers have seen the benefits decline over the past 10 years due to increased production costs and decreased selling prices.

Among the other factors of degradation are urbanization, quarries, and the firing of field and road edges. Excessive and recurrent droughts have exhausted the seed stocks of some farmers, and this could have affected the range of landraces as well as the within-population diversity. Another factor that could contribute to the loss of local agrobiodiversity is the limited transfer of indigenous knowledge from generation to generation, as we witnessed the lack of interest of new generations in rural areas to work or invest in agriculture.

Technological Options

The technological, institutional, and policy options advocated by the present project, to alleviate the major factors of degradation and the main constraints to the sustainability of local agrobiodiversity and prevent land degradation, are presented below.

Under harsh conditions prevailing in the dryland and mountainous areas of WANA, intensified agriculture and the expression of the potential of improved genetically uniform varieties could be limited by specific abiotic or biotic constraints, by their high costs, or by the long-term observed nonsustainability of the alternative land uses. Only low-cost technologies were demonstrated to improve productivity of landraces. The seed cleaning and treatment against seed-transmitted diseases have showed yield gains of 17-80% in wheat, barley, lentil, and chickpea. Similarly, early planting and the introduction of cereal/food or feed legume rotations are more advantageous. These techniques will conserve the genetic base of the local population and will improve as well the quality of the products. In the case of fruit trees, water harvesting combined with pruning and application of integrated pest and disease management can improve productivity and the quality of fruits.

For wild relatives in rangelands, water harvesting techniques are highly suitable along with reseeding and application of phosphorus fertilizer. The plantation of native palatable shrubs and the use of feed blocks produced using the by-products of the farm can contribute significantly to reducing the pressure on native vegetation during critical periods.

Among the technological options, there are tremendous opportunities for increasing the benefits from local products through processing, packaging, and labeling provided that these are accompanied by actions of public awareness, marketing, and improved hygiene. Most of the landraces have known quality and taste advantages, and their biological and organic nature could be exploited. The project has provided training mainly to women on jam, compotes, and syrup production, and introduced for the first time these products from wild plums, arbutus, and zizyphus fruits.

Alternative Sources of Income

The target areas are located close to historical sites in most cases. This has offered opportunities for marketing local products to visitors, and the project has helped in getting permission for the establishment of agrobiodiversity shops and markets. The experience of ecotourism launched by the project between the private operator in Beirut and the local community in Ham proved highly beneficial. Local communities and especially women were trained in honey and mushroom production, nursery creation and management, cultivation of medicinal, herbal, and aromatic plants, and dairy products, with emphasis on hygiene and technical backstopping provided to the private business-oriented initiatives.

Institutional and Policy Options

The empowerment of local communities is a key issue for successful management of shared resources such as water, forest, and rangeland. Responsibility for management and improvement should be devoted to local communities, with monitoring and technical supervision by government institutions. The formation of NGOs and cooperatives should be encouraged. Incentives and facilities for loan acquisition and marketing might be needed in the initial period to implement established management plans. The governments should also favor rural development actions in the remaining biodiversity-rich areas. Strict regulations are needed to prevent unsustainable land use practices and inappropriate farming activities leading to land degradation and loss of agrobiodiversity. Nurseries and informal seed increase using landraces and the wild relatives should be encouraged. Governments and development projects should encourage the use of native species in the reforestation efforts and landscape management. In extreme cases of continued degradation and loss of biodiversity threatening the whole ecosystem, restrictive measures including the establishment of natural reserves could be the best temporary option before a sound and agreed management plan can be applied.

All of these measures should be accompanied by targeted research activities using the integrated natural resources management approach, and by continuous efforts of increasing awareness of the general public and key decision-makers on the importance of preserving biodiversity. It is also recommended that community or government genebanks be created to ensure the *ex situ* conservation of valuable genetic resources.

Conclusion

Local agrobiodiversity is still the basis of the existing traditional farming systems under harsh conditions prevailing in the drylands and mountainous areas, and has potential to contribute significantly to diversification and improvement to the income of farmers and herders. Caution and restrictive measures will be needed when nonsustainable and destructive alternative land uses threaten the few remaining biodiversity-rich areas. Nonagricultural income-generating activities as well as some form of incentives or rewards, in the form of rural development actions, might be essential within any sustainable livelihood strategy for the custodians of biodiversity of global significance. Mechanisms for equitable benefit sharing advocated by many international agreements need to be developed and applied. Opportunities and facilities for exporting local products could be one of the mechanisms. Special attention should be devoted to preserving the few remaining areas rich in biodiversity of global significance, or of species that can be of high value when trying to overcome the negative effects of global warming. Appropriate techniques are available preventing land degradation and need to be transferred and adopted by farmers, NGOs, and government and nongovernment development projects. GIS tools can be instrumental in monitoring land degradation and biodiversity loss, and can be used efficiently in designing suitable land uses.

Acknowledgments

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References

Adams, C.R., and H. Eswaran. 2000. Global land resources in the context of food and environment security. pp. 35-50. In "Advances in Land Resources Management and 20th Century," 655 pp. Eds. S.P. Gawande *et al.*, New Delhi: Soil Conservation Society of India.

Awni, Y.T. 2002. Climatic and agroecological desertification in Jordan, pp 78-89. In Desert and Dryland development: Challenges and Potential in the New Millennium. Rayan, J. (ed.). Proceeding of the Sixth International Conference on the Development of Dry Lands, 22-27 August 1999, Cairo, Egypt, ICARDA, Aleppo, Syria xiv+655pp.

El-Beltagy, A. 2002. Reversing Desertification: The Potential for Research, pp. xi-xiv. In Desert and Dryland development: Challenges and Potential in the New Millennium. Ryan, J. (ed.). Proceeding of the Sixth International Conference on the Development of Dry Lands, 22-27 August 1999, Cairo, Egypt, ICARDA, Aleppo, Syria xiv+655pp.

Frankel, O. 1978. Conservation of crop genetic resources and their wild relatives: an overview, pp. 123-149. In Conservation and Agriculture (J.G. Hawkes, ed.) Duckworth, London, U.K.

Harlan, J.R. 1992. Crops and Man. Am. Soc. of Agron. Inc. Madison. Wisconsin, U.S.A., 284 pp.

Hawkes, J.G. 1983. The Diversity of Crop Plants. Harvard University Press, Cambridge, Massachusetts and London, U.K. 184 pp.

ICARDA. 1997. Conservation, Management and Sustainable Use of Dryland Biodiversity within Priority Agro-Ecosystems of the Near East. Highlights of the Proceeding of the Workshop. 54 pp.

UNCED. 1992. United Nations Conference on Environment and Development, Rio de Janeiro: UN.

World Bank. 2002. Reaching the rural poor: A rural strategy for the Middle East and North Africa region. Rural Development, Water, Environment and Social Group, World Bank, Washington, D.C., USA.

Section 5

Human Health

Chapter 19

Gene Manipulation Technology and HumanHealth: Ethical and Social Considerations

Effat A. Badr

Introduction

Modern genetics offers major opportunities to enhance the well-being of people. Recombinant DNA technology–the capacity to edit DNA–was made possible through a number of discoveries in the late 1960s and early 1970s. Genes can be added to or subtracted from an organism, or we can change the way it works by non-sexual processes. Scientists are now able to tailor DNA molecules, creating ones that have never been seen in nature. New strains and/or new products can thus be produced. This is based on the fact that all life on Earth uses the same basic genetic systems. In the past 25 years, DNA technology has had a profound effect on medical practice, as well as on many areas of biological sciences, with agriculture, industry, and environmental science being the most affected.

Achievements and Promises of DNA Technology in Health Care

The human genome contains the key to our humanity. It is the great set of assembly instructions that governs the development of every individual. In the mid 1980s, the possibility of sequencing the genome was first discussed. The Human Genome Project (HGP) came about in response to the need for efficient disease gene mapping and isolation. DNA methodologies are the key for mapping of human genes (Lewin, 2000).

The Human Genome Project is an extraordinary technological achievement. A completed draft of sequencing the 3.1 billion base pairs was announced on June 26, 2000. This initiated a whole new era in our understanding of how organisms are put together and how they operate, and what it is that sets us apart biologically from other species. Gene structure, mapping, and function are now better understood (Badr, 2003).

The Human Genome Project is a marvelous new weapon against disease. At present, however, the most powerful weapons are diagnostics (Poste, 2003). Presymptomatic diagnosis and carrier detection help predict and possibly prevent disease. So does diagnosis of genetic, infective, and malignant diseases as well as prenatal diagnosis. Pre-implantation tests, first performed in 1989, give choices to patients at an early stage. The choice of whether to be tested is best left to each individual or parent, who will directly bear the burden of genetic knowledge. In the case of prenatal diagnosis, it is the prospective mother who should make the decision, because she is the one who will bear the consequences. Genetic knowledge will remain frightening to some so long as we remain in the present intermediate stage, possessing the power to diagnose but not to cure. For example, we would not worry about testing for predisposition to Alzheimer's disease if we already had a cure (Watson and Berry, 2003). Genetic disorders can cause unthinkable misery to families. Having developed the tests, it is unconscionable not to make their existence known, inexcusable not to make them universal. It would greatly reduce the long-term social and financial burden of genetic diseases on society.

DNA fingerprinting has solved many mysteries in forensic medicine. The identity of an individual is determined beyond any doubt. Paternal disputes, for example, are now accurately resolved, such as in the recent Asian tsunami case of the lost child in Sri Lanka.

The production of useful human proteins, for example insulin, interferon, and growth hormones, came through DNA technology. Monoclonal antibodies (MAbs), after decades of disappointment, are just now coming into their own. Genentech now markets Herceptin, an MAb that targets certain forms of breast cancer. Intelligent drug design should permit more specific targeting of cell receptors so that only the relevant one is blocked. Researchers are now closing in on drugs that can target only those key proteins, many of them growth factors and their receptors, that promote cancer cell growth and division (Watson and Berry, 2003).

The potential of gene therapy is great. However, it may yet be a long way from delivering the miracles foreseen at the dawn of the genetic revolution. The first successful gene therapy was carried out at the National Institutes of Health (NIH) in 1990. The genetic disorder was adenine deaminase deficiency (ADA) in which the lack of an enzyme disables the immune system. Viruses are efficient genetic vectors. Genetic engineering has produced retroviruses that are as safe as possible for gene therapy (Lyon and Gorner, 1995). In spite of delivering too little during its first 10 years of existence, there has been some progress in gene therapy in recent months with hemophilia, SCID (severe combined immunodeficiency syndrome), and Parkinson's disease. In the near future, it should be possible to use stem cells present in umbilical cord blood or bone marrow to produce nerve cells. By transplanting these cells into the brains of patients suffering from Parkinson's disease, it may be possible to improve their condition. Another possibility is injecting the gene coding for interleukin into a brain tumor called glioblastoma, eliminating the tumor cells. This experiment proved successful in mice, and it may open the way to successful treatment of humans (Winnacker, 2003).

Ethical Dilemmas and the Poor

A central ethical challenge for DNA technology is whether it can be acceptable to intervene so profoundly in nature and the nature of human beings. The word "unnatural," frequently used, is not a valid ethical criterion. Over the ages, humans have always intervened and tampered with nature, and we cannot use the limits imposed by nature as an excuse for setting ethical limits. On the other hand, we cannot simply allow everything that is technically possible for fear of causing profound harm to our world (Winnacker, 2003).

Application of the information from the human genome project presents ethical issues for the individual and society, most notably in the area of molecular testing. These issues include those of immediate practical relevance, such as population screening; who owns and should control genetic information with respect to privacy and confidentiality; should it be used by employers and/or insurance companies. There is also the psychological impact and potential stigmatization of persons following genetic testing. Prenatal screening offers a stark choice for any woman carrying a fetus that has tested positive for a genetic disorder–to terminate or not to terminate the pregnancy. Advocacy groups insist on fetus rights, claiming that prenatal testing promotes the abortion of the affected fetuses. Issues need to be resolved with regard to appropriateness and fairness of the use of genetic technologies and HGP information. We also need to prioritize the use of public resources, and to consider commercial involvement and property rights, especially with regard to patenting. Public debate is essential and overdue. A quick and simple resolution of many of these complex issues is unlikely (Watson and Berry, 2003).

Gene therapy is an exciting and promising application of HGP data, although it has so far delivered little. Concerns are centered around the possibility that it could be used for eugenic purposes. Even for innocent purposes, will it be exclusively for use by the rich, be they individuals or countries? Gene therapy limited to somatic cells is viewed universally as ethically acceptable. Genetic modification involving the germ line is now banned by governments. Ensuring informed consent on the part of patients is essential.

Intellectual property issues and biopatenting constitute major challenges. When U.S. President Clinton and, U.K. Prime Minister Blair announced the near completion of the human genome sequence, they stipulated that the raw genome data must be placed within 24 hours in public databases, and cannot be patented. This caused a major drop in the biotechnology market, showing how sensitive this market is.

The European Directive on Legal Protection of Biotechnological Inventions article 5 stipulates on the one hand that: “The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions.” And on the other hand, that: “An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.”

In other words, a gene or sequence can be patented if a technological process produces it, but not otherwise. One fact not mentioned in the directive is that a gene can have more than one function, and can operate as part of a network of interacting genes and proteins. Proteins can associate in organized structures. This raises an important question: should someone who has discovered a gene for one particular function, and is able to produce it by biotechnology own that gene, for the next 20 years, for functions that have not yet been discovered (Winnacker, 2003)?

Article 6 of the above-mentioned directive stipulates that: Inventions shall be considered unpatentable where their commercial exploitation would be contrary to public order or morality; however, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation. The following, in particular, shall be considered unpatentable:

a) Processes for cloning human beings.
b) Processes for modifying the germ line genetic identity of human beings.
c) Uses of human embryos for industrial or commercial purposes.
d) Processes for modifying the genetic identity of animals, which are likely to cause them suffering without any substantial medical benefit to humans or animals, and also animals resulting from such processes.

The costly biotechnological advances in health care have, in the face of limited resources, resulted in greater inequalities in health care. Many people feel that applications of DNA technology are driven by commercial pressures of the biotechnology industry. Cost-benefit arguments can be persuasive in business, but take no account of the fundamental human and social issues that are often involved.

The vaccine and drug industry is reluctant to invest in biotechnological research for diseases prevalent in developing countries, because of the limited purchasing power in these countries. Of the 1233 drugs that were approved in the last decade, only 11 were for treating tropical diseases, and of these half were intended for livestock, not humans (Serageldin, 2003).

Poor countries and populations need ethical intervention. Health care should be executable on an ethical basis respecting:

- The needs of the deprived.
- Respect for moral values and equity.
- Social balance between the more needy and the economy.

Genomics and public health was the subject of a comprehensive report prepared by WHO (2002). The report refers to the likelihood that pharmaceutical companies may ignore some diseases of people in developing countries, because they also do not expect to make money from new biotechnology-based/derived vaccines or from drugs that treat the diseases (Brown, 2002).

Challenges for Developing Countries

Research and development varies from one country to another, generally depending on the educational and economic levels as well as on political stability. Lack of funding, national expertise, and access to databases, as well as weak health care systems, are the major challenges facing developing countries, but other factors are also involved (African Center for Technology Studies, 2001). Developing countries face many challenges in harnessing and applying science and development for human benefit, including:

- Economic strength is in direct relation to excellence in scientific research, with a bearing on industrial competitiveness. Excellence in scientific research is an expensive undertaking that most developing countries cannot afford. Everyday needs leave little room for investing in the future. This has kept many countries in the grip of scientific stagnation, and consequently poverty and political unrest.
- Science and technology policy bodies in many countries are not linked to other agencies and processes for economic development, public health management, environmental management, and other aspects of life. They often fail to influence such policy initiatives as the formulation of "Poverty Reduction Strategies."
- Science and technology policy studies constitute a growing part of economic and political governance in industrial countries. Most developing countries have not devoted resources to science and technology policy studies.
- The production of biotechnology-based products needs teamwork and networking between experts in various fields of science and industry, using an array of modern tools. It is therefore more challenging in those developing countries with limited manufacturing capacity.
- In many developing countries there is an almost total disconnect between science and industrial activities; local industries generally purchase technology and related know-how from abroad.
- The limited financial and human resources in many developing countries are often not targeted to national priority problems.
- Globalization will further intensify the challenges facing developing countries. The gap between developing and industrial countries continues to widen. Advanced medical technologies such as gene therapy, diagnostics, and targeted drugs are developed at high cost. Intellectual property rights will increase the cost of health care, and thus be unaffordable to patients in developing countries. Actually this is the case for the poor worldwide (Badr, 2003).

Role of Developing Countries

WHO (2002) warns that developing countries could lose out on health benefits of genomic research unless action is taken now to strengthen their participation. It

emphasizes that without a critical mass of qualified people, proper regulation, and ethical guidelines in developing countries, the research could actually widen the gap between the rich and the poor. Partnerships, improved systems of management, and public support will certainly help in these countries.

Responsibility of the Industrial Countries

The underdevelopment of some parts of the world is depriving humanity of precious human resources. There are many talented individuals in those countries who are wasting their potential in an effort to stay alive. Industrial countries should accept their share of responsibility toward the developing countries, and show international solidarity. The real needs of the populations should be considered. Vaccines, diagnostics, and drugs must be available and accessible for diseases prevalent in these countries, such as AIDS and malaria. Ethical investments have an important role to play in this context, and are crucial to the development of new treatments for which the market is relatively small, and which are not expected to yield high profits. Appropriate biotechnology transfer is also needed. The economic, cultural, and environmental status of developing countries must be seriously considered when introducing new biotechnology. Scientific cooperation between industrial and developing countries promotes the advancement of biotechnology. International nongovernmental organizations and other civil society organizations can foster such international cooperation for the transfer of technology. Differential pricing of drugs and diagnostics should be considered, to overcome the problem of cost of health care being increasingly out of reach of patients in developing countries (Badr, 2003).

Conclusion

The new life sciences, notably genetics, are helping us to gain a new understanding of life and nature. Can we use these new insights to limit the technically feasible to what is ethically tolerable? A new sense of responsibility should prevail. Human dignity and human rights need to be preserved. Debates and discussions amongst scientists, governmental and industrial communities, as well with the community at large are essential. Collective political will of the scientifically more advanced countries is needed to sustain major action to help build scientific excellence for the benefit of all. All countries and communities, rich and poor, should share the enormous advantages offered by the new life sciences revolution. Benefits of science must be available to all.

References

African Centre for Technology Studies. 2001. Report on the 1st Roundtable on Science and Technology in the Age of Globalization.

Badr, E.A. 2003. Post-genomic health advances and its implications in developing countries. In: Serageldin, I., and Persley, G.J. (eds.) Biotechnology and Sustainable Development: Voices of the South and North. CAB International, Wallingford, UK. p. 163-172.

Brown, P. 2002. Poor countries could lose out on benefits of genomic research. British Medical Journal, 324, 1053.

Lewin, B. 2000. Genes VII. 7th edn. Oxford University Press, Oxford.

Lyon, J., and P. Gorner. 1995. Altered Fates: Gene Therapy and Retooling of Human Life. W.W. Norton & Co., N.Y.

Poste, G. 2003. Commercial and practical realities of genetic diagnostics. The World Science Forum, Biovision, Lyon, France, April 8-11.

Serageldin, I. 2003. Science and the poor. In: Serageldin, I., and Persley, G.J. (eds.) Biotechnology and Sustainable Development: Voices of the South and North. CAB International, Wallingford, UK. p. 19-27.

Watson, J.D., and A. Berry. 2003. DNA: The Secret of Life. 1st edn. Alfred A. Knopf, N.Y.

WHO. 2002. Genomics and public health. WHO Advisory Committee on Health Research. World Health Organization, Geneva, Switzerland.

Winnacker, E.L. 2003. The US biotechnology industry is a mature industry; the European biotechnology industry is a growing one. Forum on Genetics and the Future of Europe, Brussels.

Chapter 20

Infectious Disease: An Enduring Threat

Peter Lachmann

Introduction

Human populations have, for many millennia, been subject to a great variety of infectious diseases. This is plausibly regarded as a consequence of the agricultural revolution which began some 10,000 years ago. Before that time human hunter/gatherers lived in small itinerant groups and kept no domestic animals, thus avoiding the problems of sewage disposal and of clean water supply. There were insufficient people to sustain major epidemic disease, and the lack of domestic animals protected them from many zoonoses. With the advent of agriculture, populations became much larger and became sedentary. They began to keep domestic animals and began to live close to them. These changes in lifestyle increased their susceptibility to infectious disease. Urbanization gave a further boost to this susceptibility.

The first major advance in combating infection was the introduction of immunization against smallpox by “variolation” (exposing a normal subject to a very small amount of scales or pus from an infected subject). This technique was invented in the Far East many centuries ago and came to European notice by way of Turkey in the early 1700s. Vaccination with cow pox–which is much safer–was introduced by Jenner at the end of the 1700s. These approaches were based on the observation made already in classical times that survivors of an infectious disease were frequently immune to further attacks of that disease, and did not require an explanation of the cause of the disease. However, no sustained improvement to the control of infectious disease was possible until the discovery of microorganisms and the acceptance of the germ theory of disease. This was in large part due to the work of Louis Pasteur (1822-95), who also disproved the spontaneous generation of microscopic life, and introduced the first vaccination using intentionally attenuated pathogens.

Combating Infectious Disease

The major strands of human activity in combating infectious disease have been:

- Public health. Ensuring a clean water supply, effective sewage disposal, and proper food hygiene; and encouraging adequate sexual hygiene. Barrier forms of contraception, such as condoms, are also of great importance in preventing the spread of infectious disease by the sexual route.
- Vaccination against infectious disease.
- Antimicrobial drugs.

Early vaccines

After the empirical introduction of vaccination in the late 1700s, no further vaccines became available until the work of Pasteur and of Koch and their groups. Most of the vaccines that are in use today were developed after the First World War (1914-18), and the rate of vaccine development in the period between 1918 and 1985 is shown in Figure 20.1. This development had an enormous effect on the infectious diseases of childhood and on major infectious diseases affecting human populations. It was particularly effective against diseases caused by bacterial toxins such as diphtheria and tetanus, and many virus diseases. Although there are some effective vaccines against bacteria, this is a somewhat more problematic subject and the vaccines generally are not quite as effective.

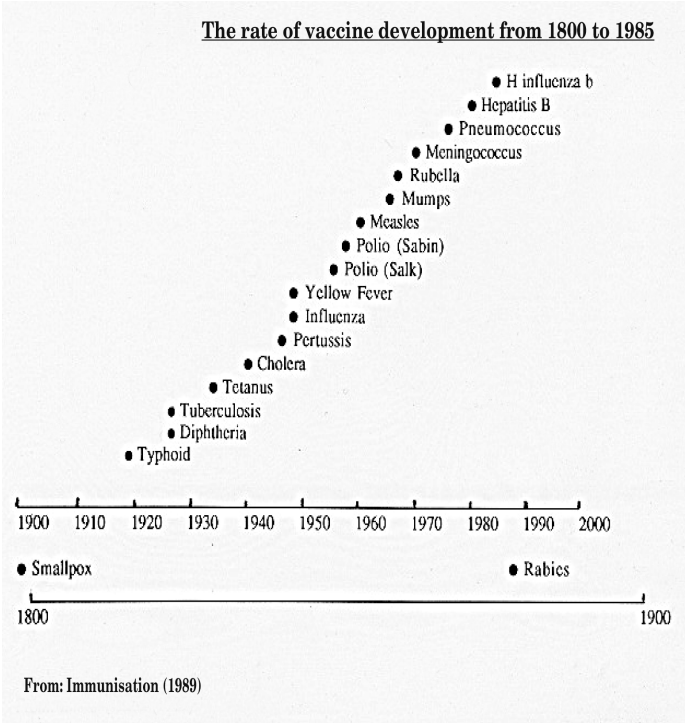

Figure 20.1. The rate of vaccine development 1800-1985.

Early antibacterial drugs

Effective antibacterial drugs appeared even later, starting with the introduction of Salvarsan by Erhlich–a great pioneer in this field–in the early 1900s. A great advance in antibacterial therapy came with the development of sulphonamides and the discovery of antibiotics in the 1930s. Antibiotics are compounds that are made by microorganisms to inhibit the growth of other microorganisms with which they share an environment, usually in the soil. The recognition that this phenomenon was widespread is really due to Rene Dubos, a Frenchman working at the Rockefeller Institute in New York, who was one of the first to institute a systematic search for antibiotics. He discovered some early antibiotics made by bacteria–bacitracin and gramicidin–which remained in topical use until recently. However, for reasons that are quite unclear, antibiotics made by bacteria tend to be toxic to mammals, and it was the chance discovery that antibiotics made by fungi (such as penicillin) or by streptomyces (such as streptomycin) can be used systemically in humans. The great period of antibiotic discovery occurred after the Second World War (1939-45), and led to a striking reduction in the morbidity and mortality of bacterial infections in humans. However, as we shall see this effect has not lasted indefinitely.

Anti-viral and anti-parasitic drugs

The isolation of drugs against virus infections was more difficult since there are no viral antibiotics, and antiviral drugs have either to be found empirically or devised from what is known about viral replication and metabolism. There are not, so far, many effective antiviral drugs. Inhibitors of viral thymidine kinase, such as acyclovir and gangcyclovir, are effective against herpes viruses that use this enzyme in their replication. Inhibitors of viral neuraminidase are effective in preventing myxovirus infections, although some of these infections produce their damage too rapidly for them to be used effectively in treatment. Drugs against eukaryotic parasites similarly had to be developed either empirically or from studies of their metabolism. Quite a few are now available, but problems with toxicity and resistance have always been a problem. Nevertheless, the development of drugs against malaria has had a great effect on the mortality from this extremely important tropical disease.

Effects on mortality rates

The effect of three strands of human activity produced a dramatic effect on mortality patterns of human populations in the industrial world. This is referred to as the "squaring off" of the death curve, which compares mortality statistics in two European cities in the 1600s and mid 1800s with those of England in the mid 1990s. The change is dramatic. In the earlier period, almost one-half of the population died before the age of 5, and of the remainder one-half were dead before the age of 40, with the survival from the age of 5 onwards declining at a linear rate. By comparison, it is now relatively uncommon to see death from natural causes before the age of 60, after which the rate rapidly increases, although life expectancy above the age of 60 has also been improving in recent decades.

Problems that Remain

In view of these dramatic improvements, why do we see an enduring threat from infectious disease? There are a number of reasons discussed below.

Public health

Adequate public health provision was never achieved in all parts of the world, and has been put under great strain by the growth of populations and the greatly increasing rate of urbanization in developing countries, with the growth of huge cities where public health infrastructure causes problems. Even where public health

infrastructure was in place, it is highly susceptible to degradation by the effects of war, civil unrest, and population movements. It is therefore not surprising that enteric infections (due to poor public health) are still a major cause of death particularly in sub-Saharan Africa (Figure 20.2).

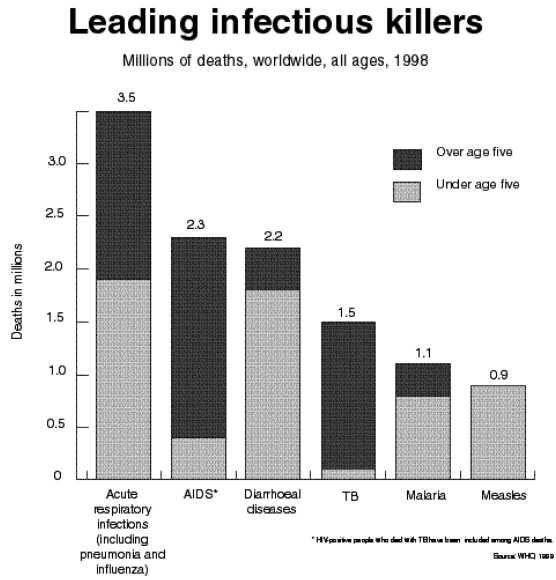

Figure 20.2. Leading infectious killers.

Vaccines

Vaccine development has also not kept up with the demand. There are a number of reasons for this. There are some microbes against which the development of effective vaccines has proved extremely difficult. Notable in this connection are organisms that make use of the strategy of antigenic variation, which makes it difficult to generate vaccines that deal with all variants. This is a problem with influenza, malaria, and HIV to mention just a few. The rate of vaccine development, has also not been helped by the intense risk averseness that afflicts vaccine development with the tendency to litigate against vaccine manufacturers if vaccines give rise to any adverse effects, either real or imagined. This proved such a problem in the United States that the federal government felt it necessary to indemnify companies producing vaccines for use in healthy children against litigation so that a supply of the necessary vaccines could be maintained. The production of a new prophylactic vaccine to be given to healthy children has become so expensive and the testing period so prolonged that only very large companies are able to undertake this work.

The resulting vaccines have become unnecessarily expensive. Recently, not least because of the generous intervention of the Bill and Melinda Gates Foundation, this situation has improved to some extent and the Global Alliance For Vaccines and Immunization (GAVI) has stimulated a considerable growth in vaccine research.

Antimicrobial drugs

Antibiotics have not proved to be quite the panacea that was first hoped. Bacteria acquire resistance to them fairly rapidly, and the rate of the discovery of new antibiotics, particularly in the last 20 years, has failed to keep up with the rate at which resistance develops. This is to a large extent the result of the original strategy of antibiotic research: seeking microbial products that inhibit the growth of other bacteria. This has become subject to the law of diminishing returns, and most of the major antibiotics that are used by microorganisms have probably been discovered. Antimicrobial research now depends substantially on the identification of new targets based on bacterial genomics, and trying to develop new classes of drugs against them. This strategy is neither enormously reliable nor enormously fast, and it is quite likely that there will be a period when there are not effective antimicrobial drugs to combat all bacterial infections.

Emerging and reemerging infections

HIV/AIDS

There has also been the emergence of new infections. The most important of these is HIV, which came to notice in the early 1980s. This infection, is transmitted sexually, or by intravenous drug abuse, or by blood products, or from mother to child, and has proved an unparalleled scourge. There are some 40 million people infected with the virus. 5 million were newly infected in 2003, in which year there were also 3 million deaths from HIV/AIDS. The distribution of the disease is not at all uniform, and it is in sub-Saharan Africa that the problem is at its most severe, although it is also serious in South and Southeast Asia and increasingly so in Eastern Europe.

HIV is a zoonotic infection that originally transferred to humans from animals. Interestingly, there were two quite separate transmission events: one occurring in East Africa where it is believed that HIV-1 infection transmitted from chimpanzees; and the other occurring in West Africa where HIV-2 is believed to have transmitted from the Sooty Mangabey. The first passage to humans of HIV-1 may have occurred as early as 1931 according to studies on viral evolution. It is not known when the first passage of HIV-2 to humans may have occurred. However, the disease in humans was not recognized before 1981, and certainly the extent of its spread must have increased rapidly about that time. An extensive collection of sera taken in the 1950s

by de Thé for studies of the Epstein Barr virus shows no antibodies to HIV-1. It is not known with certainty what caused the transmission to humans. A journalist, Edward Hooper, suggested that HIV-1 contaminated oral polio vaccines. However, this theory is not tenable because oral polio vaccine was introduced too late to account for the findings of the viral evolution. Additionally, chimpanzee cells were not used to make the vaccine, and no HIV was found in the remaining vials of vaccine. It has further been shown recently that the lentivirus found in East African chimpanzees is not closely similar to HIV-1. Nor would the theory account for the origin of HIV-2. It seems more likely that some secular change in the relations between monkeys and humans is responsible. It was suggested in 1990 by Karpas that a plausible cause would be the increasing use by African traditional healers (who use monkey products) of syringes and needles that allowed monkey tissue to be injected into humans. This would certainly have facilitated the spread of viruses such as HIV. However, this is the sort of theory that, while plausible, is extremely difficult to prove (see Philosophical Transactions of the Royal Society: Biological Sciences, Volume 356, Number 1410 2001 for references to this topic).

The development of potent anti-retroviral drugs has been a great triumph, and allows people who are infected with HIV to have longer and healthier lives. However, other than inhibiting the transmission of infection from mother to fetus, this treatment is not an effective way of stemming the epidemic. This will depend either on the development of a vaccine or on suitable lifestyle changes. It is extraordinary how difficult it has proved to make people adopt safer sexual practices or to avoid the problems of intravenous drug abuse. There is a large contribution waiting to be made here by the social scientists.

SARS

The most recent newly emerging disease is the severe acute respiratory syndrome or SARS, an infection caused by a corona virus that appears to have transferred from Civets in China to people. Fortunately the disease has so far not proved to be highly contagious, and the control measures that have been put in place have succeeded in limiting its spread. However, the infectivity of viruses is known to increase in epidemics, and it would be wrong to be complacent about the containment of SARS. Continued vigilance is necessary, and it is encouraging that a vaccine is being developed.

Influenza

Old and well-known infections also continue to be a problem. Influenza is an infection that periodically causes massive epidemics. The greatest was the epidemic of 1918 when more than 20 million people died. New influenza epidemics arise from

re-assortment of genes between influenza viruses usually in birds, and where these acquire the capacity to infect humans new antigenic variants can prove extremely dangerous. A renewed outbreak of a strain of avian influenza has occurred in ducks and chickens during the last few years and is highly dangerous when passed from birds to humans. So far, this variant has not acquired the ability to spread between humans. If it were to do so, this would be a dangerous new variant of influenza with the capacity to cause a severe epidemic. Influenza is very much more contagious than the corona virus causing SARS and its containment would be much more difficult. Vaccines are being prepared, but are so far not available.

Tuberculosis

Another old scourge that is giving rise to serious concerns is tuberculosis. The decline in tuberculosis was achieved by effective antibiotics, and by the use of surgery to remove irreversibly damaged parts of infected lungs. This has been effective in reducing tuberculosis in large parts of the industrial world. There are, however, uncontained epidemics, for example in Southern Africa, and the situation is made worse by the prevalence of HIV, which allows tuberculosis to flourish. There has also been a worrying rise in tuberculosis in the states of the former Soviet Union. Infection with TB is not easily avoided if one is in close contact with infected people, and there have even been cases arising as a result of air travel where there was a passenger with active TB. The situation is worrying, and it will be necessary to continue the search for more effective anti-tuberculous drugs as resistance increases to the existing drugs.

Infectious diseases have not gone away, and are unlikely to do so. “The price of freedom is eternal vigilance,” and this applies equally to freedom from infectious disease.

Chapter 21

Tuberculosis Research: The Promise of Genetics and Biotechnology–Scientific and Ethical Issues

Stefan Ehlers and Sahar Aly

Introduction

Respiratory infections are among the deadliest world-wide, with tuberculosis (TB) holding an ignominious first place as the single bacterial agent claiming the highest death toll per year (WHO, 2004b). Approximately one-third of the world population is infected with the causative organism *Mycobacterium tuberculosis*. Every day, almost 25,000 people develop active TB and 5000 die of the disease. This adds up to well over 8 million new cases, and almost 2 million deaths yearly. In 1993, the World Health Organization (WHO) declared TB a global emergency.

Importantly, the incidence of TB–the number of new cases per 100,000 population–is grossly uneven in its distribution. Every year, 5 million new cases occur in Southeast Asia and the Western Pacific, 2 million in Africa, 1 million in the Middle East, and 500,000 in South America. Only a few hundred thousand new cases appear in prosperous North America and Western Europe (WHO, 2004b). The death toll is almost entirely borne by the developing countries, with the brunt of the epidemic affecting Africa and Southeast Asia (Table 21.1).

The internationally recommended strategy for TB treatment and control developed by WHO is known as DOTS (Directly Observed Treatment Short-Course). It is comprised of five key components: government commitment to sustained tuberculosis control; case detection by sputum microscopy; standardized treatment for 6-8 months; regular supply of essential tuberculosis drugs; and standardized reporting system (Maher and Mikulencak, 1999). By the end of 2000, 148 of 210 countries were implementing the DOTS strategy, which has produced an average cure rate of 80% where it was used (WHO, 2002). However, it reached only 27% of the world's TB patients, and the rate of progress in case-finding between 1999 and 2000 was no faster than the average since 1994. If left untreated, one person with infectious TB will infect an average of 12-20 people, of whom 2-4 will develop infectious TB.

Table 21.1. Estimated TB incidence and mortality, 2002 (source: WHO 2004b).

	Number of cases (thousands)		Cases per 100,000 population		Deaths from TB (including TB deaths in people infected with HIV)	
WHO region	All forms (%)	Smear-positive	All forms	Smear-positive*	Number (thousands)	Number (thousands)
Africa	2354 (26)	1000	350	149	556	556
The Americas	370 (4)	165	43	19	53	53
Eastern Mediterranean	622 (7)	279	124	55	143	143
Europe	472 (5)	211	54	24	73	73
Southeast Asia	2890 (33)	1294	182	81	625	625
Western Pacific	2090 (24)	939	122	55	373	373
Global	8797 (100)	3887	141	63	1823	1823

Multidrug-resistant tuberculosis (MDR-TB) is the disease caused by mycobacteria resistant to at least isoniazid and rifampicin, the two most powerful anti-tuberculosis drugs. Drug-resistant tuberculosis arises from inconsistent or partial treatment, due to a lack of medical care and a follow-up system (WHO, 2004b). Countries of Eastern Europe are severely affected, with, in some regions of the former Soviet Union, up to 50 % of the isolates being resistant to first-line drugs. Tuberculosis patients in parts of Eastern Europe and Central Asia are ten times more likely to have multidrug-resistant tuberculosis than in the rest of the world (WHO, 2004a). Given the increasing trend toward globalization, transnational migration, and tourism, all countries are potential targets for outbreaks of multidrug-resistant tuberculosis. This alarming rate of a practically incurable TB epidemic has finally helped increase funding rates for TB research and attract capable scientists eager to explore new horizons linking basic and applied biosciences.

The promise of genetics as one of the keys to the solution stems from the fact that the genome of the human host as well as the genome of *M. tuberculosis* have been fully sequenced and annotated in the past decade. Therefore, these two genomes can now be understood in molecular terms (Cole *et al.*, 1998; Lander *et al.*, 2001). In addition, the new high-throughput methodologies now available to genetic epidemiologists and molecular microbiologists allow for the analysis of large sample numbers directly acquired in the field. For example, DNA preparations from the

blood of exposed but healthy, and therefore relatively resistant, individuals can be compared to the genetic makeup of diseased patients. New genes involved in the pathogenesis and protection against disease can thus be identified. Likewise, *M. tuberculosis* can be cultured from the sputa of patients, and the isolates from different regions in the world can then be analyzed for their genetic fingerprint. Hopefully this will reveal new clues to why some are drug-resistant, or why some are more virulent and spreading more rampantly than others. Finally, insight into the genetic makeup of both host and mycobacterium can be used to identify targets for vaccination, for example by combining immunodominant antigens with immunostimulating adjuvants, to achieve a higher or longer-lasting degree of a protective immune response. This represents an unprecedented interdependence of basic research strategies (molecular biology, genetics, biochemistry, pharmacology, epidemiology) and the "resources" of the diseased, but ultimately beneficiary population, in developing countries.

Human Genomics: Defining Genetic Resistance and Susceptibility to TB

Only 10% of those exposed to *M. tuberculosis* actually develop tuberculous disease, suggesting a potent influence of the host's genetic makeup in combating disease. A re-evaluation of early studies in mono- and dizygotic twins confirmed that genetic factors significantly predispose to disease development (Comstock, 1978). It is also well acknowledged that Afro-Americans are more susceptible to infection and disease with *M. tuberculosis* than Americans of Caucasian decent, for example (Stead *et al.,* 1990). However, not until recently have specific genes been associated with resistance and susceptibility to TB (Table 21.2).

There are two approaches to identifying these genes. The first is hypothesis-driven, based on insight gained from in vitro experiments and animal models, and capitalizes on the functions of certain molecules demonstrated to be of relevance in these assay systems. Then, polymorphisms or differential gene expression are evaluated for the genes in question in cohorts of diseased TB patients and healthy control groups. For example, the mannose binding protein (MBP) and the mannose-fucose receptor are involved in the binding and ingestion of mycobacteria into macrophages. In a case control study performed in The Gambia, low MBP plasma concentrations weakly correlated with protection against TB (Bellamy *et al.,* 1998c). Similarly, Vitamin D–due to the immunostimulatory activity of its active metabolite, 1,25-dihydroxy-Vitamin D3, on macrophages–has long been thought to participate in the immune defense against TB. A genetic variant of the Vitamin D receptor associated with decreased bone mineralization was indeed significantly underrepresented in patients with TB, pointing to an antimycobacterial protective effect of Vitamin D (Bellamy *et al.,* 1999).

Table 21.2. Examples of genes associated with resistance and susceptibility to TB.

Gene (Locus)	Evidence	Function	Reference
Nramp (Bcg)	Mouse positional cloning, Human cohort study	Divalent cation pump in phagolysosome	(Vidal et al,. 1993); (Skamene *et al.*, 1998); (Hill, 1998); (Delgado *et al.*, 2002)
Mannose binding protein	Human cohort study	Binding of mannosylated cell wall structures of mycobacteria; phagocytosis	(Bellamy *et al.*, 1998a)
Vitamin D receptor	Human cohort study	Macrophage activation	(Bellamy *et al.*, 1999)
Ubiquitin ligase UBE3A (15q31-q33)	Human linkage study	T cell activation ?	(Cervino *et al.*, 2002)
IFN-γ	Mouse model; Human cohort study	Macrophage activation; variation affects NF-κB binding site in IFN-γ promoter	(Rossouw *et al.*, 2003)
(Trl-4)	Mouse model; Human cohort study	Several candidate genes, e.g. GM-CSF-receptor	(Mitsos *et al.*, 2003)
LIX	Mouse gene expression profiling	CXCR-2 ligand, Granulocyte recruitment	(Keller *et al.*, 2004)

In mice, a heightened level of innate resistance against *M. bovis* BCG infection is mediated by a single dominant locus called bcg. The gene within this locus conferring the phenotype was identified by positional cloning, named "natural resistance associated macrophage protein 1" (*Nramp1*), and a single point mutation (which causes a change of glycine to asparagine in position 169 of the polypeptide chain) was confirmed to convert the entire resistant phenotype into a susceptible one (Skamene *et al.*, 1998). Again, in the relatively large case control study performed in The Gambia, some variants of the human *Nramp1* genes were found to be significantly associated with TB disease (Bellamy *et al.*, 1998b).

Interferon-gamma (IFN-γ) is the most potent macrophage-activating cytokine, and, indeed, in a case-control study of 313 TB cases, a highly significant association between a polymorphism (+874A-->T) in ifn-γ and tuberculosis was noted in a South African population (Rossouw *et al.*, 2003). In contrast, common haplotypes in the IFN-γ-receptor were not associated with TB in a Gambian population (Awomoyi *et al.*, 2004). Although IL-10 is the major regulatory cytokine counteracting the influence of IFN-γ, none of the known promoter variations in the IL-10 gene were correlated with the development of TB (Lopez-Maderuelo *et al.*, 2003).

The second approach to identifying genes of relevance for resistance and susceptibility to TB is an unbiased, genome-wide search for genetic polymorphisms coupled with disease. This approach was made possible by the identification of a large number of polymorphic markers within the human genome, so that

discriminating between gene variants became unequivocal. The first genome-wide linkage analysis was performed in 173 sib pairs in The Gambia and South Africa, and–although the results failed to gain statistical significance–a region on the long arm of chromosome 15 and the long arm of the X-chromosome were suggested to be coupled to disease development (Bellamy *et al.,* 2000). A putative candidate gene within this locus is UBE3A, a ubiquitin ligase. The exact mechanism of action of this gene in the pathogenesis of TB remains ill-defined (Cervino *et al.,* 2002). Genome-wide linkage analyses are currently being performed worldwide with large cohorts of well-characterized patient groups, and should yield a number of novel genetic loci and specific gene variants associated with TB.

Genetic markers may, in the relatively near future, give attending physicians insight into whether a particular TB patient may be relatively resistant to chronic disease, and therefore have a favorable prognosis when properly treated.

Ethical issues in human genome research related to TB

The US Commission for the Protection of Human Subjects of Biomedical Research has laid down fundamental principles of ethical behavior for scientists in the so-called Belmont Report (Department of Health, 1979). These include: respect for persons, beneficence, and justice. The African Malaria Network has formulated several precisions on the topic. For example, they have stated that a local ethical review board needs to be installed, and procedures need to be in place to obtain and document informed consent (AMANET, 2003). How can these stipulations be implemented in basic research projects?

In a project funded by the German Genome Research Network, the Bernhard-Nocht-Institute and the Research Center Borstel are currently conducting large-scale association studies in Ghana, where more than 2000 DNA samples have been collected from TB patients. They will be compared, by genetic analyses, with 2000 samples from exposed, but healthy controls, often living in the same family or house. One obvious ethical conundrum in this extremely valuable research project is that the target population itself is unlikely to benefit from the knowledge gained within the foreseeable future. Also, the concept of basic research is largely unfamiliar to this population, making it extremely difficult to obtain a truly informed consent. We have been careful to translate what we aim to do into familiar terms with the help of translators fluent in the local language, but we cannot be sure that we have been successful.

However, a possible failure to grasp the relevance of this basic research by the target population should not necessarily preclude our doing this study, because multiple beneficial side-effects come into play. First, patients are carefully diagnosed in the clinic, and X-rays are provided to household contacts to make sure that no disease goes undetected and reservoirs of infection are uncovered. Second, clinical follow-up, even in remote areas, is guaranteed over a period of two consecutive

years, to make sure that no other cases develop after initial exposure. Third, the best available medication is provided with DOTS as the standard therapy against tuberculosis.

A laboratory was built and fully equipped in Kumasi, where technicians were trained in the cultivation of mycobacteria and the diagnostic staining of sputum samples. This helped increase the medical standards of the region, and helped build the capacity of local researchers and institutions to deal with the TB epidemic themselves. In addition, mycobacterial isolates are shipped to the National Reference Center for Mycobacteria in Borstel, where large-scale drug susceptibility testing is performed. This has resulted, for the first time in Ghana, in establishing the level of isoniazid or multidrug resistance patterns, for example. It would appear that this is a good example of a mutually beneficial arrangement. Basic scientists can learn from what is happening at the population level, in terms of what the genetic make-up of those resistant vs. those susceptible to TB is like. The local community, as equal partners, can benefit from medical diagnosis, therapy, and preventive follow-up, which in its state-of-the-art form can then be maintained long after the study period is over.

Mycobacterial Genomics: The Gateway to New Drug Targets for Curing TB

Chemotherapy for TB began in the late 1940s with the advent of streptomycin. The introduction of isoniazid (INH), rifampin (RMP), and pyrazinamide (PZA) shortened the duration of therapy from 18 to 9 months, and then to the current 6-month regimen. A successful treatment that eradicates the bacilli and prevents the development of drug-resistant strains, necessitates the application of multiple drugs in adequate dosages on a regular basis, for a sufficient period, and with expert monitoring. Under the WHO-recommended DOTS regime, drugs should reach every TB patient free of charge (Niemann and Rüsch-Gerdes, 2003). When patients, after treatment with the standard regimens, are not cured and their mycobacteria show in vitro resistance to at least RMP and INH, they constitute the group of multidrug-resistant tuberculosis (MDR-TB) patients.

Potential new tuberculosis drugs fall into two categories. The first is off-the-shelf drugs with anti-tuberculosis activity that can be enhanced further. These tend to be far quicker to develop, but may not be active against MDR-TB. The second category is novel compounds developed specifically for TB. These will take longer to develop. Off-the-shelf drugs are fluoroquinolones, rifamycins, oxazolidinones, and experimental compounds are nitroimidazopyran and novel quinolones (Médecins sans frontières, 2004).

DOTS-Plus for MDR-TB is under testing and development through pilot projects and operational research conducted by members of the international Stop-TB Working Group (WG) on DOTS-Plus for MDR-TB. DOTS-Plus involves the use

of alternative (or, second-line) drugs to combat MDR strains. However, there is a real need for third-line drugs, or better still new first-line drugs to combat MDR-TB and possibly shorten the overall course of chemotherapy.

The relatively recent availability of tools to analyze M. tuberculosis at the molecular level have made possible a great advance in the understanding how this microorganism uses its cellular signalling and transcriptional machinery to survive. The completion of the genome sequence of the H37Rv strain in 1998 (Cole *et al.*, 1998), as well as advances in genetic techniques such as the generation of knock-out mutants, provided a burst of information, highlighting and exploiting the unique features of M. tuberculosis.

Genes involved in general virulence, disease pathogenesis, adaptation and growth within the host, or mycobacteria-specific pathways, such as enzymes involved in lipid metabolism or cell wall biosynthesis, could be new targets for antimicrobial drug discovery (Table 21.3). Because the cell wall components and the proteins producing them are unique for the pathogen, many of the current first-line antitubercular drugs and chemotherapeutics in development target proteins involved in building and maintaining the mycobacterial cell wall.

Table 21.3. Examples of novel drug targets emerging from characterizing the TB genome.

Target	Gene	Encoding	Functional involvement	Inhibitors	Reference
Cell wall biosynthesis	rmlC	dTDP-6-deoxy-D-xlyo-4-hexulose reductase	Rhamnose pathway	2, 3, 5, tri-substituted-4-thiazolidinones	(Babaoglu *et al.*, 2003)
	glf	UDP-galactopyranose mutase	Cell wall arabinan biosynthesis	320KAW73 uridine-based enzyme inhibitor	(Soltero-Higgin *et al.*, 2004); (Scherman *et al.*, 2003)
	mmaA4	SAM-dependent methyl transferases	Synthesis and modification of mycolic acids of the cell wall by introduction of cyclopropane rings and methyl branches		(Dubnau *et al.*, 2000); (Barry *et al.*, 1998)
	pcaA	Methyl transferase	Cording, Synthesis of mycolic acid cyclopropane ring		Glickman *et al.*, 2000)
	mmpL7	Membrane transporters	Synthesis and transport of phthiocerol dimycocerosate		(Cox *et al.*, 1999)
	lspA	Lipoprotein signal peptidase	Lipoprotein processing	Globomycin	(Sander *et al.*, 2004)
	pks (1-18)	Polyketide synthase	Complex cell wall-associated fatty acid synthesis		(Saxena *et al.*, 2003)
Metabolic pathways	lysA	Mesodiami-nopimelate decarboxylase	Final step of lysine biosynthesis	Difluoromethyl ornithine	(Pavelka and Jacobs, 1996); (Bacchi *et al.*, 1980)

Table 21.3: (continued)

Target	Gene	Encoding	Functional involvement	Inhibitors	Reference
	def	Peptide de-formylase	Catalysis of the deformylation reaction of N-terminal residues of newly synthesized proteins	Actinonin, BB-3497 metalloenzyme inhibitor	(Clements *et al.*, 2001); (Chen *et al.*, 2000)
	pyrR	Regulatory protein	Pyrimidine nucleotide biosynthesis	Pyrimidine analogues	(Kantardjieff and Rupp, 2004)
	fadD and fadE	Fattty acyl AMP ligase, Acyl-CoA-synthase	Fatty acid b-oxidation system, lipid synthesis		(Cox *et al.*, 1999); (Trivedi *et al.*, 2004)
	dfrA	Dihydrofolate reductase	Variety of biochemical functions involving single carbon transfer in folate pathway	Antifolate compounds, Br-WR99210	(Schweitzer *et al.*, 1990); (Li *et al.*, 2000)
	panC and panD	Panthothenate synthase	Biosynthesis of panthothenate (vitamin B5)		(Sambandamurthy *et al.*, 2002)
	glnA1	Glutamine synthase	Nitrogen metabolism		(Tullius *et al.*, 2003)
	mbtB	Mycobactins (2-hydroxyphenyl-oxazoline con-taining sidero-phore molecules)	Iron acquisition		(De Voss *et al.*, 2000)
Persistence	icl	Isocitrate lyase	Glyoxalate shunt, metabolism of fatty acids	3-nitropropion-ate, 3-bromo-pyruvate	(Sharma *et al.*, 2000)
	relMtb		Stringent response during nutrient starvation, synthesis of (p)ppGp		(Primm *et al.*, 2000)
	dnaE	Main replicative DNA polymerase	DNA repair, DNA synthesis		(Boshoff *et al.*, 2003)
	hsp70	Heat-shock protein 70		Induced overexpression	(Stewart *et al.*, 2001)
Virulence	SecA (1+2)	Accessory secretion factor	Secretion systems, e.g. for superoxide dismutase A		(Braunstein *et al.*, 2003); (Braunstein *et al.*, 2001)
	Plc (C+D	Phospholipases	Cleaving of phosphatidylcholine		(Johansen *et al.*, 1996)
	sigH	Sigma factor H	Control of regulated set of genes		(Kaushal *et al.*, 2002)
	phoP-phoQ	Two-component regulatory proteins	Intracellular replication		(Perez *et al.*, 2001)
	hbhA	Heparin-binding hemagglutinin	Dissemination to extra-pulmonary sites		(Pethe *et al.*, 2001)
	erp	Repetitive protein	Intracellular replication		(Berthet *et al.*, 1998)
	katG	Catalase peroxidase	Detoxification of oxygen intermediates		(Li *et al.*, 1998)

As mycolic acids are structural components of the mycobacterial cell wall, inhibitors of the enzymes involved in the biosynthetic pathway of mycolates should be particularly useful anti-mycobacterial drugs. Isoniazid (INH; isonicotinic acid hydrazine) is the oldest drug effective in the treatment of tuberculosis and, once converted to its active metabolite by catalase within the mycobacterium, targets enoyl-ACP-reductase (inhA), catalyzing the NADH-dependent reduction of the trans double bond between the C2 and C3 positions on fatty acyl substrates of length C16 or greater (Ducasse-Cabanot *et al.,* 2004; Miesel *et al.,* 1998). Diazoborines and triclosan are InhA inhibitors, but due to their poor solubility (McLeod *et al.,* 2001) and substantial toxicity (Grassberger *et al.,* 1984), they are not widely used. On screening for inhibition of *M. tuberculosis* InhA, two novel piperazine analogues could be identified (Kuo *et al.,* 2003).

Mycobacterium tuberculosis differs from other pulmonary pathogens in the fact that it establishes a latent state (Gomez and McKinney, 2004), during which its long-term survival depends on the glyoxalate shunt. Isocitrate lyase and malate synthase together form the glyoxalate shunt which is activated during oxygen starvation (Wayne and Hayes, 1996;Wayne and Lin, 1982), bypassing CO_2 in the tricarboxylic acid cycle, which oxidizes acetate to ATP. The shunt allows *M. tuberculosis* and other bacteria to synthesize carbohydrates from fatty acids. Thus, isocitrate lyase could be a potential drug target to combat persistent, or latent, infections, and would therefore be particularly useful in preventing reactivation TB. The structure of icl without ligand and in complex with two inhibitors, 3-nitropropionate and 3-bromopyrovate, has already been solved (Sharma *et al.,* 2000), facilitating further modeling studies.

Further analysis of the TB genome has revealed that there are a number of protein families like PE (proline-glutamate) and PPE (proline-proline-glutamate) or the related PE-PGRS, which are unique in mycobacteria and whose coding DNA constitutes approximately 5% of the total coding DNA of *M. tuberculosis* (Brennan and Delogu, 2002). Their function is still unknown, but as they are highly regulated during in vivo persistence (Chan *et al.,* 2002), these protein families may prove to be superior drug targets.

The two-component systems form a large family of proteins involved in signal transduction that allow bacteria to detect and respond to many different kinds of stimuli. Studies employing animal and cell models of virulence show that several two-component system mutants result in an altered phenotype (attenuated or hyper-virulent). For example, the DosR/DosS/DosT regulon comprises a two-component signaling system that is required for the *M. tuberculosis* genetic response to hypoxia and nitric oxide, two conditions that produce reversible growth arrest in vitro and may contribute to latency in vivo (Roberts *et al.,* 2004). Two-component systems involved in bacterial survival and multiplication within the host can be seen as a novel class of flexible drug targets, as they are not only quite distinct from the regulatory systems of mammalian cells, but may be intercepted at multiple steps in their signal transduction cascade (Tyagi and Sharma, 2004).

To date, less than 1% of newly identified genes in *M. tuberculosis* have been exploited in their potential as novel drug targets. Although developing them through clinical trials to full market appearance may take more than a decade, it is encouraging to anticipate that there may finally be a new mycobacteriocidal drug after the introduction of the last one, rifampin, in 1967.

Ethical issues in susceptibility testing and antimycobacterial therapy related to TB

Before novel drugs can be appropriately tested on the target population that needs them most, regional patterns of drug susceptibility of *M. tuberculosis* complex strains need to be ascertained. In another project the Research Center Borstel is participating in, a diagnostic laboratory in Nukus, Uzbekistan, was established in a collaborative effort with Médecins sans frontières. The Aral Lake region is one of the hardest hit in terms of multi-drug resistance of *M. tuberculosis* strains, but since no exact figures have been available, it has remained largely unknown what drugs should be used as first-line therapy in patients newly diagnosed with TB. A laboratory was therefore fully equipped with the necessary machinery for cultivating mycobacteria to perform drug susceptibility testing for both first-line and second-line drugs. Most importantly, Borstel personnel spent some time in Nukus to train the local personnel to become experts in performing such routine tests. Because of an extensive study on more than 400 patients and TB isolates, the most useful initial therapy in Nukus is now known. Also, permanent quality control of the drug testing performed in Usbekistan is provided by the Borstel Research Center, which serves as the international reference laboratory.

In partnership with the “Green Light Committee” established by the Working Group on DOTS-Plus for MDR-TB within WHO (a board that oversees the adherence to treatment guidelines upon which the approval of funding is contingent), The Global Fund to Fight AIDS, Tuberculosis and Malaria–a partnership between governments, civil society, the private sector and affected communities–makes money available to buy and distribute second-line drugs to those 14% of patients in the region that have acquired strains resistant to treatment with first-line drugs.

It is important to emphasize that, as basic scientists, we do not necessarily become involved in these types of studies because we are overly altruistic or believe in the common good. We want to learn how certain strains of *M. tuberculosis* spread, how they acquire drug resistance traits, and we want to learn from the strains successful in the field so that we may handle them better when they arrive in our own countries. Therefore, in exchange for being granted permission to obtain that knowledge by genetic analysis of the strains successful in the field, we provide our expertise in diagnostic mycobacteriology, pay for equipment maintenance, and return to Nukus from time to time to supervise the maintenance of the now achieved relatively high level of diagnostic and therapeutic standards.

This kind of reciprocity will also be most beneficial for the introduction of novel drugs to treat TB in areas where there is a high frequency of strains that are multidrug resistant. Access to new antimycobacterially active drugs must be ensured for populations participating in drug trials until long after the trials are over. Funding and distribution issues should be settled even before trials start. It is to be hoped that pharmaceutical companies and research consortia cooperate with agencies such as Médecins sans frontières, Global Fund, STOP TB, and others that have a long-standing expertise in this area. These groups have developed the necessary competence and skills to involve local authorities and health care workers in providing the necessary infrastructure.

It is unlikely that pharmaceutical companies will divert major resources to TB drug development, because those most affected will not be able to afford the new drugs, if priced to make a profit. In principle, however, there is no rule against "ethical" pricing strategies, allowing patent erosion in developing countries where generics could be produced and distributed at significantly lower cost. This is currently happening in India, Brazil, and South Africa for drugs related to HIV therapy, and may well become the way of the future. If properly advocated, it could even be a novel marketing strategy for pharmaceutical companies. They could advertise their "ethical" involvement in developing countries to combat major diseases at production cost, while charging the people in industrial countries at market prices.

Another important issue concerns the allocation of scarce resources within developing countries. Is it better to utilize all funds to institute a nationwide DOTS strategy, knowingly neglecting those few percent that have multi-drug resistant TB? Or is it more important to concentrate on treating patients with MDR strains that, when continuing to spread throughout a population, ultimately threaten to make all DOTS strategies futile? Treatment for MDR is 50 to 500 times more expensive than DOTS, and often requires hospitalization, laboratory follow-up, and long-term supervision. There is no simple "either-or" solution to this problem. It will be imperative to convince all countries to implement DOTS, bearing as much of the cost as they can, and find supranational strategies (for example, involving WHO, STOP-TB, Médecins sans frontières, and others) to detect, isolate, and treat patients with MDR-TB. In this respect it may be worthwhile to concentrate on certain subpopulations whose treatment may prove to be particularly cost-effective.

On any given day, it is estimated that the world's prisons hold 8-10 million people. However, 4-6 times this number pass through prisons each year, because of the high turnover. Prison conditions can fan the spread of disease through overcrowding, poor ventilation, poor nutrition, and inadequate or inaccessible medical care. The level of TB in prisons has been reported to be up to 100 times higher than in the general population. Cases of TB in prisons may account for up to 25% of a country's burden of TB. Of major concern is the very high levels (of up to 24 % of all cases) of MDR-TB that have been reported from some prisons (Bone *et al.*, 2000). Control of TB can be effective, even in prisons (Rodrigo *et al.*, 2002), when programs are based on reducing the diagnostic delay to a minimum, controlling

adherence to therapy using DOT, minimizing the number of patients lost to follow-up, and tracing the maximum number of contacts.

Functional Genomics for Vaccinating Against TB

The failure of the BCG vaccine strain, which is essentially an attenuated version of a once fully virulent mycobacterium, to protect against pulmonary tuberculosis is far from being completely understood. However, basic research has revealed a number of shortcomings of this vaccine strain that may be amenable to improvement by genetic engineering (Table 21.4). For example, Behr *et al.*, (1999) have shown that BCG lacks important antigens that are recognized by an effective immune response. Therefore, one of the current strategies to make a better BCG is to introduce some of these antigens back into the vaccine to make it more immunogenic (Horwitz *et al.*, 2000; Pym *et al.*, 2003). It has also been speculated that BCG may not induce the right mixture of specific immune cells in the host (Kaufmann, 2001). Therefore, genetic manipulation is used to make a BCG that will do this more effectively (Hess *et al.*, 1998). Finally, it is thought that the ineffectiveness of BCG in developing countries stems largely from the fact that environmental and somewhat related mycobacteria interfere with BCG, because they hinder its replication, which is necessary to induce a protective immune response (Brandt *et al.*, 2002). One highly promising branch of research tries to build a so-called subunit vaccine consisting of certain antigens of *M. tuberculosis* in an isolated form and mixing them with immunostimulating adjuvants to induce protective immunity (Brandt *et al.*, 2000; Doherty *et al.*, 2002). In addition, a vaccine-boost scenario is currently being entertained as the most likely strategy to build on residual immunity induced by BCG, and to strengthen it by a second vaccination with selected antigens from the *M. tuberculosis* complex. In this setting, the injection of plasmid DNA encoding for selected mycobacterial antigens appears particularly promising (Feng *et al.*, 2001;Tanghe *et al.*, 2001).

Table 21.4. Examples of novel vaccine strategies in tuberculosis research.

Vaccine type	Strategy	Advantages	Reference
Modified BCG	Auxotrophic mutants Improved safety	Improved safety	(Guleria *et al.*, 1996); (Sambandamurthy *et al.*, 2002)
	Recombinant, expressing cytokines	Enhanced Th1 response	(Murray *et al.*, 1996)
	Recombinant, expressing selected antigens	Improved immunogenicity	(Horwitz *et al.*, 2000); (Pym *et al.*, 2003)
	Recombinant, expressing hemolysin	Enhanced CD8 response	(Hess *et al.*, 1998)
Attenuated *M. tuberculosis*	Auxotrophic mutants	Increased safety ?	(Smith *et al.*, 2001); (Sambandamurthy *et al.*, 2002)
	Defined cell wall and metabolic mutants	Decreased persistence; enhanced immunogenicity due to altered host response	(Berthet *et al.*, 1998); (Yuan *et al.*, 1998); (McKinney *et al.*, 2000); (Glickman *et al.*, 2000); (Cox *et al.*, 1999); (Kaushal *et al.*, 2002)
Subunit	Protein plus adjuvant	High safety; standardized regimen; mild side effects	(Horwitz *et al.*, 1995); (Brandt *et al.*, 2000); (Horwitz *et al.*, 2000); (Olsen *et al.*, 2001); (Coler *et al.*, 2001)
	DNA vaccine	Enhanced CD8 response	(Tascon *et al.*, 1996); (Huygen *et al.*, 1996); (Coler *et al.*, 2001)
	Live vector	Enhanced CD8 response	(McShane *et al.*, 2001); (Hess *et al.*, 2000)
Combination of above in defined temporal regimen	Prime-boost	Improved immunogenicity	(Tanghe *et al.*, 2001); (McShane *et al.*, 2001); (Feng *et al.*, 2001); (Brooks *et al.*, 2001)

Ethical issues in vaccine trials against TB

Tuberculosis is a chronic disease, and even if an individual is infected today, disease may only become apparent after several years, sometimes decades. Thus, vaccine trials take a long time to determine which ones are truly effective. If basic research is successful and can define those genes that correlate with resistance or immunity, it may become possible to use surrogate markers for protection; this would considerably reduce the time necessary to show vaccine efficacy. If epidemiological linkage analyses are successful, and can define which genes determine progression of disease, one might be able to identify those individuals in a population that are most likely to come down with disease. Then by selecting the most susceptible subjects and testing the vaccine on them, the number of people required to show efficacy may be reduced to a more manageable size. In this way, participants in association studies currently performed in high-incidence countries (see above) may yet reap the benefit of results obtained in these studies.

Who is going to pay for the vaccine trials? Although there is a huge target population, the market size is relatively small, because the current BCG vaccine is so cheap. An agreement will therefore be necessary to stagger the pricing for any new vaccine. If it costs say Euro 50 in the North, and Euro 4 in the South, the annual world market has been calculated to swell to approximately 600 million Euro, and may therefore become attractive to pharmaceutical companies. The European Union has made a clinical trial platform one of its priorities, and will spend a considerable amount of funds for testing TB vaccines. It is of utmost importance that protocols and infrastructure are developed so that a full-scale phase III trial in Africa or Asia can be performed.

There are a number of ethical issues that need to be addressed before conducting these trials (Snider, 2000):

- Is it necessary to do trials of TB vaccines in one or more developing countries? Although it may be highly desirable to test a vaccine where TB has its highest incidence, an enormous infrastructural network and a structured process of ethical review needs to be in place; this may not be feasible in several of the least developed countries.
- Should a standard BCG vaccine group be included as a control? BCG reliably offers a moderate to high level of protection to children without prior *M. tuberculosis* infection in terms of preventing disseminated, fatal disease. A placebo control group, although perhaps scientifically desirable, might therefore incur unacceptably high fatalities. On the other hand, BCG can cause disseminated disease in HIV-infected individuals, and a placebo control might be more appropriate.
- Should tuberculin skin-test screening be performed and preventive therapy be offered to skin-test positive individuals? Naturally, if the vaccine candidate to be tested results in tuberculin reactivity after vaccination, skin-test screening is

probably meaningless in terms of diagnosing TB. However, if the vaccine candidate does not lead to tuberculin skin test conversion, skin-test screening would identify those recently infected with tuberculosis, and preventive treatment in the form of isoniazid should be instituted. If, however, the trial endpoint is to determine whether the vaccine protects against disease (not just infection), skin testing should not be performed, but some groups (such as HIV-infected individuals) may run a risk of increased adverse events due to delayed diagnosis.

- How can researchers, vaccine manufacturers, and international and national health organizations ensure that trial results are appropriately available to the study population after the trial ends? This is the most important political issue, and scientists have generally not felt responsible for addressing this point. However, it needs to be stressed that scientists do have a responsibility to consider what will happen after a vaccine trial is over. If the population participating in the trial has no chance of benefiting from the trial results (for example, because the successful vaccine is too expensive to be administered on a population-wide basis in a developing country), then the ethical justification for including this population in the trial should be seriously questioned. There is need for a firm commitment from the start, via organizations such as WHO or the European Union, that a successful vaccine will be manufactured and distributed free of charge to the developing countries, so that the global epidemic can be brought to an end.

Conclusion

There is currently no alternative to basic research in tuberculosis. The times when we could hope to eliminate TB by large-scale chemotherapy are unfortunately over, because in the meantime a new TB–with multidrug-resistant strains–is lurking out there.

What is truly novel and most exciting is the marriage of biotechnology and genetics with epidemiological research at the population level in the field. This is, in a way, basic research returning to its roots, and this will be where groundbreaking results can be achieved, by studying what is truly happening in the field, and not only in the laboratory. Tuberculosis probably results from the complex interplay of several genetic host variants in concert with genetically diverse makeup of the causative microorganism. Only a more detailed definition of the genetic background of both host and microbe will ultimately yield a clear understanding of this interrelationship.

A partnership between basic researchers in the North, and the beneficiary population in the South, will help provide clues for a strategy to eradicate TB. Respect and justice within this partnership will bring sustained medical improvement to developing countries as an immediate benefit.

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References

AMANET. 2003. AMANET Performance Report November 2001-December 2003. Newsletter of the African Malaria Network Trust (AMANET) 13. http://www.amanet-trust.org.

Awomoyi, A.A., S. Nejentsev, A. Richardson, J., Hull, O. Koch, M. Podinovskaia, J.A. Todd, K.P. McAdam, J.M. Blackwell, D.Kwiatkowski, and M.J. Newport. 2004. No association between interferon-gamma receptor-1 gene polymorphism and pulmonary tuberculosis in a Gambian population sample. Thorax 59, 291-294.

Babaoglu, K., M.A. Page, V.C. Jones, M.R. McNeil, C. Dong, J.H. Naismith, and R.E. Lee. 2003. Novel inhibitors of an emerging target in Mycobacterium tuberculosis; substituted thiazolidinones as inhibitors of dTDP-rhamnose synthesis. Bioorganic and Medicinal Chemistry Letters 13, 3227-3230.

Bacchi, C.J., H.C. Nathan, S.H. Hutner, P.P. McCann, and A. Sjoerdsma. 1980. Polyamine metabolism: a potential therapeutic target in trypanosomes. Science 210, 332-334.

Barry III, C.E., R.E. Lee, K. Mdluli, A.E. Sampson, B.G. Schroeder, R.A. Slayden, and Y. Yuan. 1998. Mycolic acids: structure, biosynthesis and physiological functions. Progress in Lipid Research 37, 143-179.

Behr, M.A., M.A. Wilson, W.P. Gill, H. Salamon, G.K. Schoolnik, S. Rane, and P.M. Small. 1999. Comparative genomics of BCG vaccines by whole-genome DNA microarray. Science 284, 1520-1523.

Bellamy, R., N. Beyers, K.P. McAdam, C. Ruwende, R. Gie, P. Samaai, D. Bester, M. Meyer, T. Corrah, M. Collin, D.R. Camidge, D. Wilkinson, E. Hoal-van Helden, H.C. Whittle, W. Amos, P. van Helden, and A.V. Hill. 2000. Genetic susceptibility to tuberculosis in Africans: a genome-wide scan. Proceedings of the National Academy of Sciences of the United States of America 97, 8005-8009.

Bellamy, R., C. Ruwende, T. Corrah, K.P. McAdam, M. Thursz, H.C. Whittle, and A.V. Hill. 1999. Tuberculosis and chronic hepatitis B virus infection in Africans and variation in the vitamin D receptor gene. The Journal of Infectious Diseases 179, 721-724.

Bellamy, R., C. Ruwende, T. Corrah, K.P. McAdam, H.C. Whittle, and A.V. Hill. 1998a. Assessment of the interleukin 1 gene cluster and other candidate gene polymorphisms in host susceptibility to tuberculosis. Tubercle and Lung Disease 79, 83-89.

Bellamy, R., C. Ruwende, T. Corrah, K.P. McAdam, H.C. Whittle, and A.V. Hill. 1998b. Variations in the NRAMP1 gene and susceptibility to tuberculosis in West Africans. The New England Journal of Medicine 338, 640-644.

Bellamy, R., C. Ruwende, K.P. McAdam, M. Thursz, M. Sumiya, J. Summerfield, S.C. Gilbert, T. Corrah, D. Kwiatkowski, H.C. Whittle, and A.V. Hill. 1998c. Mannose binding protein deficiency is not associated with malaria, hepatitis B carriage nor tuberculosis in Africans. The Quarterly Journal of Medicine 91, 13-18.

Berthet, F.X., M. Lagranderie, P. Gounon, C. Laurent-Winter, D. Ensergueix, P. Chavarot, F. Thouron, E. Maranghi, V. Pelicic, D. Portnoi, G. Marchal, and B. Gicquel. 1998. Attenuation of virulence by disruption of the Mycobacterium tuberculosis erp gene. Science 282, 759-762.

Bone, A., A. Aerts, M. Grzemska, M. Kimerling, H. Kluge, M. Levy, F. Portaels, M. Raviglione, and F. Varaine. 2000. Tuberculosis in Prisons. In 'Tuberculosis Control in Prisons: A Manual for Programme Managers.' (World Health Organization and International Committee of the Red Cross: Geneva.)

Boshoff, H. I., M.B. Reed, C.E. Barry III, and V. Mizrahi. 2003. DnaE2 polymerase contributes to in vivo survival and the emergence of drug resistance in Mycobacterium tuberculosis. Cell 113, 183-193.

Brandt, L., M. Elhay, I. Rosenkrands, E.B. Lindblad, and P. Andersen. 2000. ESAT-6 subunit vaccination against Mycobacterium tuberculosis. Infection and Immunity 68, 791-795.

Brandt, L., C.J. Feino, O.A. Weinreich, B. Chilima, P. Hirsch, R. Appelberg, and P. Andersen. 2002. Failure of the Mycobacterium bovis BCG vaccine: some species of environmental mycobacteria block multiplication of BCG and induction of protective immunity to tuberculosis. Infection and Immunity 70, 672-678.

Braunstein, M., A.M. Brown, S. Kurtz, and W.R. Jacobs, Jr. 2001. Two nonredundant SecA homologues function in mycobacteria. Journal of Bacteriology 183, 6979-6990.

Braunstein, M., B.J. Espinosa, J. Chan, J.T. Belisle, and W.R. Jacobs, Jr. 2003. SecA2 functions in the secretion of superoxide dismutase A and in the virulence of Mycobacterium tuberculosis. Molecular Microbiology 48, 453-464.

Brennan, M.J., and G. Delogu. 2002. The PE multigene family: a 'molecular mantra' for mycobacteria. Trends in Microbiology 10, 246-249.

Brooks, J.V., A.A. Frank, M.A. Keen, J.T. Bellisle, and I.M. Orme. 2001. Boosting vaccine for tuberculosis. Infection and Immunity 69, 2714-2717.

Cervino, A.C., S. Lakiss, O. Sow, R. Bellamy, N. Beyers, E. Hoal-van Helden, P. van Helden, K.P. McAdam, and A.V. Hill. 2002. Fine mapping of a putative tuberculosis-susceptibility locus on chromosome 15q11-13 in African families. Human Molecular Genetics 11, 1599-1603.

Chan, K., T. Knaak, L. Satkamp, O. Humbert, S. Falkow, and L. Ramakrishnan. 2002. Complex pattern of Mycobacterium marinum gene expression during long-term granulomatous infection. Proceedings of the National Academy of Sciences of the United States of America 99, 3920-3925.

Chen, D.Z., D.V. Patel, C.J. Hackbarth, W. Wang, G. Dreyer, D.C. Young, PS. Margolis, C. Wu, Z.J. Ni, J. Trias, R.J. White, and Z. Yuan. 2000. Actinonin, a naturally occurring antibacterial agent, is a potent deformylase inhibitor. Biochemistry 39, 1256-1262.

Clements, J.M., R.P. Beckett, A. Brown, G. Catlin, M. Lobell, S. Palan, W. Thomas, M. Whittaker, S. Wood, S. Salama, P.J. Baker, H.F. Rodgers, V. Barynin, D.W. Rice, and M.G. Hunter. 2001. Antibiotic activity and characterization of BB-3497, a novel peptide deformylase inhibitor. Antimicrobial Agents and Chemotherapy 45, 563-570.

Cole, S.T., R. Brosch, J. Parkhill, T. Garnier, C. Churcher, D. Harris, S.V. Gordon, K. Eiglmeier, S. Gas, C.E. Barry III, F. Tekaia, K. Badcock, D. Basham, D. Brown, T. Chillingworth, R. Connor, R. Davies, K. Devlin, T. Feltwell, S. Gentles, N. Hamlin, S. Holroyd, T. Hornsby, K. Jagels, and B.G. Barrell. 1998. Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence. Nature 393, 537-544.

Coler, R.N., A. Campos-Neto, P. Ovendale, F.H. Day, S.P. Fling, L. Zhu, N. Serbina, J.L. Flynn, S.G. Reed, and M.R. Alderson. 2001. Vaccination with the T cell antigen Mtb 8.4 protects against challenge with Mycobacterium tuberculosis. Journal of Immunology 166, 6227-6235.

Comstock, G. W. 1978. Tuberculosis in twins: a re-analysis of the Prophit survey. American Review of Respiratory Disease 117, 621-624.

Cox, J.S., B. Chen, M. McNeil, and W.R. Jacobs Jr. 1999. Complex lipid determines tissue-specific replication of Mycobacterium tuberculosis in mice. Nature 402, 79-83.

De Voss, J.J., K. Rutter, B.G. Schroeder, H. Su, Y. Zhu, and C.E. Barry III. 2000. The salicylate-derived mycobactin siderophores of Mycobacterium tuberculosis are essential for growth in macrophages. Proceedings of the National Academy of Sciences of the United States of America 97, 1252-1257.

Delgado, J.C., A. Baena, S. Thim, and A.E. Goldfeld. 2002. Ethnic-specific genetic associations with pulmonary tuberculosis. The Journal of Infectious Diseases 186, 1463-1468.

Department of Health, E. a. W. 1979. Ethical Principles and Guidelines for the Protection of Human Subjects of Research. In 'The Belmont Report.' (National Institutes of Health: Bethesda, Maryland.).

Doherty, T.M., A.W. Olsen, L. van Pinxteren, and P. Andersen. 2002. Oral vaccination with subunit vaccines protects animals against aerosol infection with Mycobacterium tuberculosis. Infection and Immunity 70, 3111-3121.

Dubnau, E., J. Chan, C. Raynaud, V.P. Mohan, M.A. Laneelle, K. Yu, A. Quemard, I. Smith, and M. Daffe. 2000. Oxygenated mycolic acids are necessary for virulence of Mycobacterium tuberculosis in mice. Molecular Microbiology 36, 630-637.

Ducasse-Cabanot, S., M. Cohen-Gonsaud, H. Marrakchi, M. Nguyen, D. Zerbib, J. Bernadou, M. Daffe, G. Labesse, and A. Quemard. 2004. In vitro inhibition of the Mycobacterium tuberculosis beta-ketoacyl-acyl carrier protein reductase MabA by isoniazid. Antimicrobial Agents and Chemotherapy 48, 242-249.

Feng, C.G., U. Palendira, C. Demangel, J.M. Spratt, A.S. Malin, and W.J. Britton. 2001. Priming by DNA immunization augments protective efficacy of Mycobacterium bovis Bacille Calmette-Guerin against tuberculosis. Infection and Immunity 69, 4174-4176.

Glickman, M.S., J.S. Cox, and W.R. Jacobs Jr. 2000. A novel mycolic acid cyclopropane synthetase is required for cording, persistence, and virulence of Mycobacterium tuberculosis. Molecular Cell 5, 717-727.

Gomez, J.E., and J.D. McKinney. 2004. M. tuberculosis persistence, latency, and drug tolerance. Tuberculosis.(Edinb.) 84, 29-44.

Grassberger, M.A., F. Turnowsky, and J. Hildebrandt. (1984). Preparation and antibacterial activities of new 1,2,3-diazaborine derivatives and analogues. Journal of Medicinal Chemistry 27, 947-953.

Guleria, I., R. Teitelbaum, R.A. McAdam, G. Kalpana, W.R. Jacobs Jr., and B.R. Bloom. 1996. Auxotrophic vaccines for tuberculosis. Nature Medicine 2, 334-337.

Hess, J., L. Grode, J. Hellwig, P. Conradt, I. Gentschev, W. Goebel, C. Ladel, and S.H. Kaufmann. 2000. Protection against murine tuberculosis by an attenuated recombinant Salmonella typhimurium vaccine strain that secretes the 30-kDa antigen of Mycobacterium bovis BCG. The Federation of European Microbiological Societies Immunology and Medical Microbiology 27, 283-289.

Hess, J., D. Miko, A. Catic, V. Lehmensiek, D.G. Russell, and S.H. Kaufmann. 1998. Mycobacterium bovis Bacille Calmette-Guerin strains secreting listeriolysin of Listeria monocytogenes. Proceedings of the National Academy of Sciences of the United States of America 95, 5299-5304.

Hill, A.V. 1998. The immunogenetics of human infectious diseases. Annual Review of Immunology 16, 593-617.

Horwitz, M.A., G. Harth, B.J. Dillon, and S. Maslesa-Galic. 2000. Recombinant bacillus Calmette-Guerin (BCG) vaccines expressing the Mycobacterium tuberculosis 30-kDa major secretory protein induce greater protective immunity against tuberculosis than conventional BCG vaccines in a highly susceptible animal model. Proceedings of the National Academy of Sciences of the United States of America 97, 13853-13858.

Horwitz, M.A., B.W. Lee, B.J. Dillon, and G. Harth. 1995. Protective immunity against tuberculosis induced by vaccination with major extracellular proteins of Mycobacterium tuberculosis. Proceedings of the National Academy of Sciences of the United States of America 92, 1530-1534.

Huygen, K., J. Content, O. Denis, D.L. Montgomery, A.M. Yawman, R.R. Deck, C.M. DeWitt, I.M. Orme, S. Baldwin, C. D'Souza, A. Drowart, E. Lozes, P. Vandenbussche, J.P. Van Vooren, M.A. Liu, and J.B. Ulmer. 1996. Immunogenicity and protective efficacy of a tuberculosis DNA vaccine. Nature Medicine 2, 893-898.

Johansen, K.A., R.E. Gill, and M.L. Vasil. 1996. Biochemical and molecular analysis of phospholipase C and phospholipase D activity in mycobacteria. Infection and Immunity 64, 3259-3266.

Kantardjieff, K., and B. Rupp. 2004. Structural bioinformatic approaches to the discovery of new antimycobacterial drugs. Current Pharmaceutical Design 10, 1-17.

Kaufmann, S.H. 2001. How can immunology contribute to the control of tuberculosis? Nature Reviews Immunology 1, 20-30.

Kaushal, D., B.G. Schroeder, S. Tyagi, T. Yoshimatsu, C. Scott, C. Ko, L. Carpenter, J. Mehrotra, Y.C. Manabe, R.D. Fleischmann, and W.R. Bishai. 2002. Reduced immunopathology and mortality despite tissue persistence in a Mycobacterium tuberculosis mutant lacking alternative sigma factor, SigH. Proceedings of the National Academy of Sciences of the United States of America 99, 8330-8335.

Keller, C., J. Lauber, A. Blumenthal, J. Buer, and S. Ehlers. 2004. Resistance and susceptibility to tuberculosis analysed at the transcriptome level: lessons from mouse macrophages. Tuberculosis (Edinb.) 84, 144-158.

Kuo, M.R., H.R. Morbidoni, D. Alland, S.F. Sneddon, B.B. Gourlie, M.M. Staveski, M. Leonard, J.S. Gregory, A.D. Janjigian, C. Yee, J.M. Musser, B. Kreiswirth, H. Iwamoto, R. Perozzo, W.R. Jacobs Jr., J.C. Sacchettini, and D.A. Fidock. 2003. Targeting tuberculosis and malaria through inhibition of Enoyl reductase: compound activity and structural data. The Journal of Biological Chemistry 278, 20851-20859.

Lander, E.S., L.M. Linton, B. Birren, C. Nusbaum, M.C. Zody, J. Baldwin, K. Devon, K. Dewar, M. Doyle, W. FitzHugh, R. Funke, D. Gage, K. Harris, A. Heaford, *et al.*, 2001. Initial sequencing and analysis of the human genome. Nature 409, 860-921.

Li, R., R. Sirawaraporn, P. Chitnumsub, W. Sirawaraporn, J. Wooden, F. Athappilly, S. Turley, and W.G. Hol. 2000. Three-dimensional structure of M. tuberculosis dihydrofolate reductase reveals opportunities for the design of novel tuberculosis drugs. Journal of Molecular Biology 295, 307-323.

Li, Z., C. Kelley, F. Collins, D. Rouse, and S. Morris. 1998. Expression of katG in Mycobacterium tuberculosis is associated with its growth and persistence in mice and guinea pigs. The Journal of Infectious Diseases 177, 1030-1035.

Lopez-Maderuelo, D., F. Arnalich, R. Serantes, A. Gonzalez, R. Codoceo, R. Madero, J.J. Vazquez, and C. Montiel. 2003. Interferon-gamma and interleukin-10 gene polymorphisms in pulmonary tuberculosis. American Journal of Respiratory and Critical Care Medicine 167, 970-975.

Maher, D., and M. Mikulencak. 1999. What is DOTS? In 'A Guide to Understanding the WHO-recommended TB Control Strategy Known as DOTS.' (World Health Organization: Geneva).

McKinney, J.D., K. Honer zu Bentrup, E.J. Munoz-Elias, A. Miczak, B. Chen, W.T. Chan, D. Swenson, J.C. Sacchettini, W.R. Jacobs Jr., and D.G. Russell. 2000. Persistence of Mycobacterium tuberculosis in macrophages and mice requires the glyoxylate shunt enzyme isocitrate lyase. Nature 406, 735-738.

McLeod, R., S.P. Muench, J.B. Rafferty, D.E. Kyle, E.J. Mui, M.J. Kirisits, D.G. Mack, C.W. Roberts, B.U. Samuel, R.E. Lyons, M. Dorris, W.K. Milhous, and D.W. Rice. 2001. Triclosan inhibits the growth of Plasmodium falciparum and Toxoplasma gondii by inhibition of apicomplexan Fab I. International Journal of Parasitology 31, 109-113.

McShane, H., R. Brookes, S.C. Gilbert, and A.V. Hill. 2001. Enhanced immunogenicity of CD4(+) t-cell responses and protective efficacy of a DNA-modified vaccinia virus Ankara prime-boost vaccination regimen for murine tuberculosis. Infection and Immunity 69, 681-686.

Medecins sans frontiers. 2004. TB care in the 21st century. In 'Running out of breath?' (Campaign for access to essential medicines: Geneva).

Miesel, L., T.R. Weisbrod, J.A. Marcinkeviciene, R. Bittman, and W.R., Jacobs Jr. 1998. NADH dehydrogenase defects confer isoniazid resistance and conditional lethality in Mycobacterium smegmatis. Journal of Bacteriology 180, 2459-2467.

Mitsos, L.M., L.R. Cardon, L. Ryan, R. LaCourse, R.J. North, and P. Gros. 2003. Susceptibility to tuberculosis: a locus on mouse chromosome 19 (Trl-4) regulates Mycobacterium tuberculosis replication in the lungs. Proceedings of the National Academy of Sciences of the United States of America 100, 6610-6615.

Murray, P.J., A. Aldovini, and R.A. Young. 1996. Manipulation and potentiation of antimycobacterial immunity using recombinant bacille Calmette-Guerin strains that secrete cytokines. Proceedings of the National Academy of Sciences of the United States of America 93, 934-939.

Niemann, S., and S. Rüsch-Gerdes. 2003. Mycobacteria and TB–Therapy and Drug Resistance. Mycobacteria and TB 2, 84-96.

Olsen, I., M. Tryland, H.G. Wiker, and L.J. Reitan. 2001. AhpC, AhpD, and a secreted 14-kilodalton antigen from Mycobacterium avium subsp. paratuberculosis distinguish between paratuberculosis and bovine tuberculosis in an enzyme-linked immunosorbent assay. Clinical and Diagnostic Laboratory Immunology 8, 797-801.

Pavelka, Jr., M.S., and W.R. Jacobs, Jr. 1996. Biosynthesis of diaminopimelate, the precursor of lysine and a component of peptidoglycan, is an essential function of Mycobacterium smegmatis. Journal of Bacteriology 178, 6496-6507.

Perez, E., S. Samper, Y. Bordas, C. Guilhot, B. Gicquel, and C. Martin. 2001. An essential role for phoP in Mycobacterium tuberculosis virulence. Molecular Microbiology 41, 179-187.

Pethe, K., S. Alonso, F. Biet, G. Delogu, M.J. Brennan, C. Locht, and F.D. Menozzi. 2001. The heparin-binding haemagglutinin of M. tuberculosis is required for extrapulmonary dissemination. Nature 412, 190-194.

Primm, T.P., S.J. Andersen, V. Mizrahi, D. Avarbock, H. Rubin, and C.E. Barry III. 2000. The stringent response of Mycobacterium tuberculosis is required for long-term survival. Journal of Bacteriology 182, 4889-4898.

Pym, A.S., P. Brodin, L. Majlessi, R. Brosch, C. Demangel, A. Williams, K.E. Griffiths, G. Marchal, C. Leclerc, and S.T. Cole. 2003. Recombinant BCG exporting ESAT-6 confers enhanced protection against tuberculosis. Nature Medicine 9, 533-539.

Roberts, D.M., R.P. Liao, G. Wisedchaisri, W.G. Hol, and D.R.Sherman. 2004. Two sensor kinases contribute to the hypoxic response of Mycobacterium tuberculosis. The Journal of Biological Chemistry 279, 23082-23087.

Rodrigo, T., J.A. Cayla, D.O. Garcia, M.T. Brugal, J.M. Jansa, R. Guerrero, A. Marco, and V. Martin.. 2002. Effectiveness of tuberculosis control programmes in prisons, Barcelona 1987-2000. The International Journal of Tuberculosis and Lung Disease 6, 1091-1097.

Rossouw, M., H.J. Nel, G.S. Cooke, P.D. van Helden, and E.G. Hoal. 2003. Association between tuberculosis and a polymorphic NFkappaB binding site in the interferon gamma gene. Lancet 361, 1871-1872.

Sambandamurthy, V.K., X. Wang, B. Chen, R.G. Russell, S. Derrick, F.M. Collins, S.L. Morris, and W.R. Jacobs Jr. 2002. A pantothenate auxotroph of Mycobacterium tuberculosis is highly attenuated and protects mice against tuberculosis. Nature Medicine 8, 1171-1174.

Sander, P., M. Rezwan, B. Walker, S.K. Rampini, R.M. Kroppenstedt, S. Ehlers, C. Keller, J.R. Keeble, M. Hagemeier, M.J. Colston, B. Springer, and E.C. Bottger. 2004. Lipoprotein processing is required for virulence of Mycobacterium tuberculosis. Molecular Microbiology 52, 1543-1552.

Saxena, P., G. Yadav, D. Mohanty, and R.S. Gokhale. 2003. A new family of type III polyketide synthases in Mycobacterium tuberculosis. The Journal of Biological Chemistry 278, 44780-44790.

Scherman, M.S., K.A. Winans, R.J. Stern, V. Jones, C.R. Bertozzi, and M.R. McNeil. 2003. Drug targeting Mycobacterium tuberculosis cell wall synthesis: development of a microtiter plate-based screen for UDP-galactopyranose mutase and identification of an inhibitor from a uridine-based library. Antimicrobial Agents and Chemotherapy 47, 378-382.

Schweitzer, B.I., A.P. Dicker, and J.R. Bertino. 1990. Dihydrofolate reductase as a therapeutic target. Federation of American Societies for Experimental Biology Journal 4, 2441-2452.

Sharma, V., S. Sharma, B.K. Hoener zu, J.D. McKinney, D.G. Russell, W.R. Jacobs, Jr., and J.C. Sacchettini. 2000. Structure of isocitrate lyase, a persistence factor of Mycobacterium tuberculosis. Nature Structural Biology 7, 663-668.

Skamene, E., E. Schurr, and P. Gros. 1998. Infection genomics: Nramp1 as a major determinant of natural resistance to intracellular infections. Annual Review of Medicine 49, 275-287.

Smith, D.A., T. Parish, N.G. Stoker, and G.J. Bancroft. 2001. Characterization of auxotrophic mutants of Mycobacterium tuberculosis and their potential as vaccine candidates. Infection and Immunity 69, 1142-1150.

Snider, D.E., Jr. 2000. Ethical issues in tuberculosis vaccine trials. Clinical Infectious Diseases 30 Suppl 3, S271-S275.

Soltero-Higgin, M., E.E. Carlson, T.D. Gruber, and L.L. Kiessling. 2004. A unique catalytic mechanism for UDP-galactopyranose mutase. Nature Structural and Molecular Biology 11, 539-543.

Stead, W.W., J.W. Senner, W.T. Reddick, and J.P. Lofgren. 1990. Racial differences in susceptibility to infection by Mycobacterium tuberculosis. The New England Journal of Medicine 322, 422-427.

Stewart, G.R., V.A. Snewin, G. Walzl, T. Hussell, P. Tormay, P. O'Gaora, M. Goyal, J. Betts, I.N. Brown, and D.B. Young. 2001. Overexpression of heat-shock proteins reduces survival of Mycobacterium tuberculosis in the chronic phase of infection. Nature Medicine 7, 732-737.

Tanghe, A., S. D'Souza, V. Rosseels, O. Denis, T.H. Ottenhoff, W. Dalemans, C. Wheeler, and K. Huygen. 2001. Improved immunogenicity and protective efficacy of a tuberculosis DNA vaccine encoding Ag85 by protein boosting. Infection and Immunity 69, 3041-3047.

Tascon, R.E., M.J. Colston, S. Ragno, E. Stavropoulos, D. Gregory, and D.B. Lowrie. 1996. Vaccination against tuberculosis by DNA injection. Nature Medicine 2, 888-892.

Trivedi, O.A., P. Arora, V. Sridharan, R. Tickoo, D. Mohanty, and R.S. Gokhale. 2004. Enzymic activation and transfer of fatty acids as acyl-adenylates in mycobacteria. Nature 428, 441-445.

Tullius, M.V., G. Harth, and M.A. Horwitz. 2003. Glutamine synthetase GlnA1 is essential for growth of Mycobacterium tuberculosis in human THP-1 macrophages and guinea pigs. Infection and Immunity 71, 3927-3936.

Tyagi, J.S., and D. Sharma. 2004. Signal transduction systems of mycobacteria with special reference to M. tuberculosis. Current Science 86, 93-102.

Vidal, S.M., D. Malo, K. Vogan, E. Skamene, and P. Gros. 1993. Natural resistance to infection with intracellular parasites: isolation of a candidate for Bcg. Cell 73, 469-485.

Wayne, L.G., and L.G. Hayes. 1996. An in vitro model for sequential study of shiftdown of Mycobacterium tuberculosis through two stages of nonreplicating persistence. Infection and Immunity 64, 2062-2069.

Wayne, L.G., and K.Y. Lin. 1982. Glyoxylate metabolism and adaptation of Mycobacterium tuberculosis to survival under anaerobic conditions. Infection and Immunity 37, 1042-1049.

WHO. 2002. http://www.who.int/inf/en/pr-2002-21.html World Health Organization Information Office: Geneva.

WHO. 2004a. http://www.who.int/mediacentre/releases/2004/pr17/en/ World Health Organization Media Center: Geneva.

WHO. 2004b. Global tuberculosis control–surveillance, planning, financing. In 'WHO Report 2004.' http://www.who.int/tb/publications/global_report/2004/en/ World Health Organization: Geneva.

Yuan, Y., D.D. Crane, R.M. Simpson, Y.Q. Zhu, M.J. Hickey, D.R. Sherman, and C.E. Barry III. 1998. The 16-kDa alpha-crystallin (Acr) protein of Mycobacterium tuberculosis is required for growth in macrophages. Proceedings of the National Academy of Sciences of the United States of America 95, 9578-9583.

Chapter 22

Vaccine Security: Ensuring the Uninterrupted Sustainable Supply of Affordable Vaccine to Children in Developing Countries

Steve Jarrett

Introduction

Vaccines play a critical role in preventing the spread of communicable diseases. They are one of the most cost-effective interventions in population-based health (World Bank, 1993). During the 1980s, through the leadership of the World Health Organization(WHO) and the United Nations Children's Fund (UNICEF), the coverage of immunization, as determined by the coverage of the third dose of Diptheria-Tetanus-Pertussis (DTP) in infants under one year old, rose from 37 to 73% (UNICEF, 2002). This level of coverage, around 70%, remained constant in the 1990s, due to the difficulty of contacting hard-to-reach populations and a general lack of funding. Today, the benefits of immunization are still not reaching all children, and more than 30 million newborns remain unimmunized every year (WHO, 2002). This means that readily available biotechnology is not benefiting all the children it could.

The global market for vaccines was estimated at US$6 billion in 2000, double that in 1992 (Greco, 2002). This market has expanded in value since then, with additional investment associated with the prevention of bioterrorism, although it still remains a very small part of the global pharmaceutical industry (valued at over US$400 billion). The basic vaccines, such as DTP, measles, oral polio vaccine (OPV), and the existing tuberculosis vaccine Bacille Calmette-Guerin (BCG), which are the principal products used in developing countries, represent less than 10% of the global market value. The general trend in the vaccine industry has been toward the private for-profit sector and on products that have the highest return on investment. Vaccines used by travelers and proprietary pediatric vaccines, such as pneumococcal and meningococcal vaccines, represent the fastest expanding sectors of the industry.

Vaccines are subject to long lead times in their production, with periods of one year not uncommon. For increases in capacity, or the commissioning of new facilities, anywhere from three to seven years are required. The cost of the development of new vaccines has reached levels similar to that of medicines, of well over US$500 million per product (Masignani *et al.*, 2003). Investment by industry is based on the certainty of markets for their products, and on a predictable and reliable demand for specific vaccines and sure funding. Developing countries, however, often have fluctuating demand from year to year, and are bound within annual budget cycle approvals and cannot plan on a multi-year basis with any great certainty (Costa *et al.*, 2003). This disconnect between the industry long-term planning requirement and the reality of developing countries short-term budget plans makes the developing countries' vaccine market a precarious one, and high risk for vaccine manufacturers that have to invest well ahead in capacity.

The tendency, therefore, has been for new products to be introduced in high-income countries, leaving the basic vaccines to developing countries. This has essentially caused a divergence in the vaccine product market. High-income countries generally use measles-mumps-rubella (MMR), accelular pertussis in DTP (DTaP), and inactivated polio vaccine (IPV). Low-income countries generally use monovalent measles, whole-cell pertussis in DTP (DTwP) and oral polio vaccine (OPV). The prices of products used in high-income countries can be as much as one hundred times the prices of equivalent products used in low-income countries, with vaccine manufacturers logically giving priority attention to high-income country markets. This divergence has erased the ability to obtain differentiated pricing between high- and low-income countries, as the products are no longer shared.

The increased focus of the vaccine industry on the most profitable segments of the vaccine market, the divergence of products between high- and low-income countries, and mergers of some of the pharmaceutical companies with vaccine production, led to a rapid decline in the number of manufacturers making basic vaccines. This decline happened even though a small number of manufacturers from developing countries entered the international market in the mid 1990s. By 2000, there were only three WHO-approved international manufacturers of DTwP, tetanus toxoid, and monovalent measles vaccines, thus causing an extremely narrow supply base. This was most clearly seen in the increasing shortages of vaccines available in the international market.

By 2001, UNICEF, which buys vaccines for about 100 countries, equal to 40% of the global volume of vaccine doses but only 5% of the market value due to the relatively low prices of basic vaccines, received vaccine offers for its tenders at only 30-50% of the volume it had been offered in the mid 1990s (Figure 22.1).

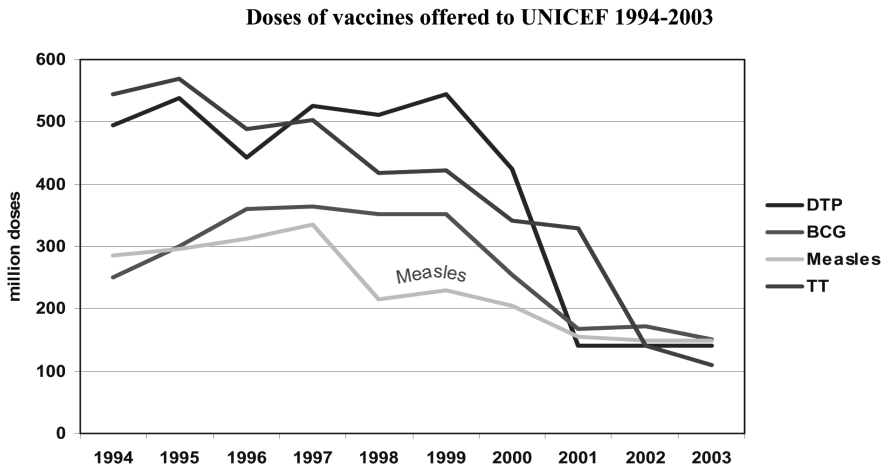

Figure 22.1. Doses of vaccines offered to UNICEF 1994-2003.
Source: UNICEF Supply Division, Copenhagen, Denmark.

These offers were very close to the purchase levels of UNICEF, thus creating no buffer between supply and demand in the case of sudden surges in demand or failure in production. In fact, between 2000 and 2002, serious delays were encountered at times in delivering vaccines to developing countries because of the very tight supply situation.

A Vaccine Security Strategy

Because of the size of the UNICEF global purchase, and its influence in low-income countries where it buys over 80% of all vaccines used, UNICEF bears significant responsibility in assuring its procurement approach best ensures long-term sustainability in the supply of vaccines. For this reason, and in answer to the tight supply situation, UNICEF pioneered a vaccine security strategy with the objective of converting the low-income countries market to one that was more predictable and reliable (Jarrett, 2002). The goal was to enter into multi-year firm commitments for vaccine purchases, to ensure availability of vaccines needed by children. To make firm commitments in purchasing, UNICEF had to address the accuracy of forecasting as well as the guarantee of the availability of resources.

In the two years since the vaccine security strategy was adopted by UNICEF in early 2002, accuracy in excess of 80% in the forecast of vaccine needs across 90

countries has been achieved, through increased analysis with countries of their vaccine and immunization situation. For global vaccine contracts entered into by UNICEF in the latter half of 2003 for the 2004-06 period for a total estimated value of US$736 million, 44% have been negotiated on a firm commitment basis for supply to developing countries (unpublished data from UNICEF Supply Division, Copenhagen, Denmark). This essentially enables a more equitable sharing of risk in the supply of vaccines to low-income countries between manufacturers and the countries. Forward funding allowing the establishment of firm commitments has come from the Vaccine Fund, which is associated with the Global Alliance on Vaccines and Immunization (GAVI), and UNICEF itself.

As a result, the offer of vaccines to UNICEF has increased, creating a buffer between supply and demand, giving a greater stability to the low-income countries market. In securing supply from up to four producers for the basic vaccines, UNICEF has had to negotiate with some manufacturers not to stop production or to re-enter production of the basic vaccines. The corresponding increased investments have meant an increase in the weighted average prices of all basic vaccines, although part of the rise is due to the increased value of the Euro against the US dollar in 2004. In essence, stabilizing the vaccine market for low-income countries, as determined by buying from at least four manufacturers with a spread of prices, has added cost but has at the same time recognized vaccine value through a willingness to pay higher prices to guarantee availability. The current situation demonstrates an increased offer of vaccine from manufacturers, but with a rising weighted average price through 2006 (Figure 22.2).

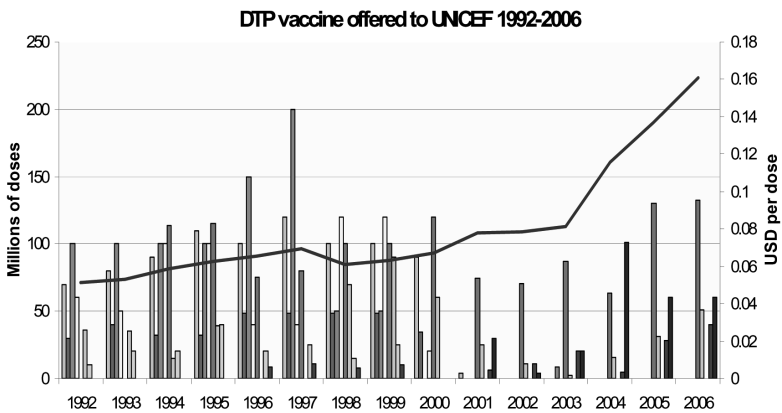

Figure 22.2. DTP vaccine offered to UNICEF 1992-2006.
Source: UNICEF Supply Division, Copenhagen, Denmark.

It is assumed that this revaluation is a one-time adjustment to ensure that a number of manufacturers produce the vaccines and remain in competition for sales to UNICEF and other buyers. In the case of DTP vaccine, for example, the revaluation comprises about 25% of the overall cost of supplying this vaccine. Without competition among manufacturers, there would be a significant risk, nevertheless, that prices would rise far beyond this 25% differential.

The influence of having a predictable demand and adequate funding for vaccines has been best illustrated in recent years by the monovalent Hepatitis B vaccine. In 2000, the Vaccine Fund received around US$1 billion in funding, most notably $750 million from the Bill and Melinda Gates Foundation(1) . The objective was to accelerate the introduction of underused and new vaccines to low-income countries, specifically Hepatitis B, Haemophilus Influenza B (Hib), and Yellow Fever vaccines. As the Hepatitis B burden was well known globally, and significant demand from countries existed, the price of the vaccine per dose fell from US$1 to around 30 US cents in 2 years, and several new manufacturers are developing Hepatitis B vaccines, as indicated in Figure 22.3.

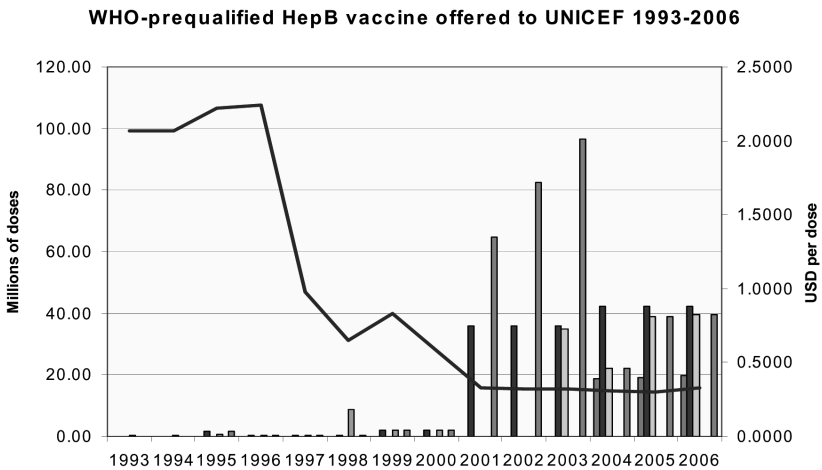

Figure 22.3. WHO-prequalified HepB vaccine offered to UNICEF 1993-2006.
Source: UNICEF Supply Division, Copenhagen, Denmark.

An oversupply of Hepatitis B vaccine rapidly ensued. Nonetheless, countries eventually opted in most cases to request the combination vaccine, DTP-Hepatitis B, given the advantages in vaccine administration by simply substituting the DTP

(1)Global Alliance on Vaccines and Immunization (GAVI), Proceedings of GAVI Board Meeting, Oslo, Norway, June 2000.

vaccine with the combination. The fact that the combination vaccine was produced by only one company and not readily available slowed down the introduction of hepatitis B to countries. It is expected that more manufacturers of this combination vaccine will be ready to deliver in 2006, thus increasing competition and achieving lower prices.

In the case of Hib, the burden of disease was less well known than Hepatitis B, it was a much more expensive vaccine whether in monovalent form or combined with DTP, and as such has not been widely introduced as yet. The combination vaccine, DTP-HepB+Hib, is currently also made by only one manufacturer, although there are already several others attempting to develop this pentavalent product. It is a more complex vaccine to make and prices are unlikely to drop until the end of the current decade, unless technological improvements are introduced.

One of the most striking aspects of the low-incomes vaccine market is that over many years funding has come mainly from donor agencies and not from the Governments themselves. In terms of vaccines purchased by UNICEF, only 5% of funding is attributable directly to Government budgets. The main sources of external support are donor agencies, such as the Centers for Disease Control of the US Government, international financial institutions such as the World Bank and the German Development Bank, and more recently the Vaccine Fund. The dilemma faced is that this dependence on external funding has worked well for the relatively inexpensive basic vaccines, although significant numbers of children still remain unimmunized every year. However, it is proving to be a much more difficult challenge with respect to sustaining the introduction of newer more expensive vaccines, because donors have so far not assured increases in long-term funding. So while the vaccine security strategy has worked for the basic vaccines, it is in doubt for newer vaccines, unless significant new money becomes available.

At stake is whether increasing the equity of access of children in low-income countries to new vaccines, essential for saving lives, is really possible. It is calculated that new vaccines could save an additional 2 million infant lives. The essence is whether advances in life-saving biotechnology can reach the poor or not, or are for the exclusive use of high-income countries.

Future Challenges

The main challenge to governments and donors is to mobilize increasing and sure future funding to guarantee access for all children to basic vaccines, as well as new biotechnology. The main challenge to the vaccine industry is to ensure vaccine production even in the uncertainty of the situation of low-income countries. National governments, donors, and the vaccine industry have to work together to ensure the vaccines needed by children around the world are readily available at prices that are affordable to countries, but that also provide a reasonable rate of return to manufacturers.

There is little doubt that vaccines are of critical importance in national health in all countries. The way forward is to create a healthy vaccine market in developing countries, particularly low-income countries where children are at greatest risk of communicable diseases. Also needed is long-term sustainable funding to ensure vaccine security for basic and newer vaccines, and motivating industry to continuously develop new vaccines and technologies needed by the poor.

The example of vaccines is illustrative of the need for biotechnological breakthroughs to consider very early in the development phase the commercial implications. These include production, the relevance of a competitive marketplace, and the ability to deliver across a wide range of country situations, to ensure ready and equitable access to all those who could benefit.

References

Costa, A. *et al.,* 2003. Determining measles-containing vaccine demand and supply: an imperative to support measles mortality reduction efforts. J. Infectious Diseases, 187 (suppl 1): S22-28.

Greco, M. 2002. The future of vaccines: an industrial perspective. Vaccine, 20: S101-3.

Jarrett, S. 2002. Vaccine Security and the Cape Town Call to Action: Vaccination for Every Child. 12 April 2002, Vaccines: Children and Practice. Vol. 6, S15-17, Adis International.

Masignani, V., Lattanzi, M., and Rappuoli, R. 2003. The value of vaccines. Vaccine, 21: S2:110-3.

UNICEF. 2002. State of the World's Children 2003. New York.

WHO. 2002. State of the World's Vaccines and Immunization. Geneva.

World Bank. 1993. World Development Report, Investing in Health. Oxford University Press.

Chapter 23

Computational Chemistry: A Powerful and Inexpensive Tool for Basic and Applied Research in the Life Sciences*

Chérif F. Matta

Introduction

With the advent of powerful computers and accurate *ab initio*[1] electronic structure and density functional theory (DFT) methods, computational chemistry has become an established branch of modern chemistry. The 1998 Nobel Prize in Chemistry was awarded to John Pople and Walter Kohn for their pioneering contributions to computational chemistry and DFT, respectively.

Chemistry is often described as the "central science": A discipline unmatched by the extent of its symbiotic relationships with other branches of science. The theory of chemistry rests entirely on physics, particularly quantum mechanics, yet chemistry itself can be viewed as the most fundamental level of many other disciplines such as: biology, pharmacology, pharmaceutical, medical and health sciences, and environmental sciences. The problem of reconciling the life sciences with their physical roots has been eloquently stated by Schrödinger (1944): "How can the events in space and time which take place within the spatial boundary of a living organism be accounted for by physics and chemistry?"

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*This chapter is not intended to be a complete review of a vast and active field of research such as computational chemistry and its applications in the life sciences. It is hoped that this chapter will spark the interest of the reader by citing a few recent contributions of computational chemistry to bioscience. The articles selected reflect my personal and professional interests.

[1]The Latin phrase ab initio means "from first principles." When linked with the phrases "quantum chemistry" or "electronic structure methods" it implies a 'pure' theoretical method that does not include arbitrary or empirical parameters except a few fundamental constants. In contrast, a semiempirical quantum chemical method is heavily parametrized, and hence is much faster but less reliable and only valid for molecules of the same type for which it has been parametrized.

The discovery of the bridge connecting chemistry (and hence biology) to its deepest underlying roots in physical theory has been a dream of several of the most eminent minds in the history of modern science. For example, one quotes an optimistic Gay-Lussac (1808): "We are perhaps not far removed from the time, when we shall be able to submit the bulk of chemical phenomena to calculation" (quoted and cited through Krogh-Jespersen, 2004); or Dirac's (1929) famous statement: "The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble." Dirac concludes his statement by asserting: "It therefore becomes desirable that approximate practical methods of applying quantum mechanics should be developed, which can lead to an explanation of the main features of complex atomic systems without too much computation."

Computational chemistry is the discipline that takes advantage of efficient algorithms and fast computers to provide approximate numerical solutions to the equations referred to by Dirac, namely, the various forms of the molecular Schrödinger equation. The solution of this equation yields the state function, *P*, which contains all the information that can be known about the system. Once an approximate *P* is obtained from the calculation, one can then extract the expectation value of any "observable" by the appropriate choice of mathematical operators that act on *P*. In this way, the state function *P* and the set of mathematical operators represent the link between theory–implemented through computational chemistry–and the real world, that is, observation.

One may ask: Why should we bother with theoretical/computational chemistry? More particularly, what is the relevance of this rather specialized branch of chemistry to "the poor" and how does it contribute to a "*BioVision*" for the future? I will address these questions sketchily to give the reader some sense of what this branch of science has to offer to improve the health and well being of humans.

Chemistry, Computer Science, and the Life Sciences

In recent times, the cross fertilization between computer science, biology, and chemistry gave rise to new and exciting fields of research. The basis for the discussion in this section is represented in the relationships between the classical fields of research and their recent-times hybrids (Figure 23.1).

Bioinformatics/computational biology is broadly defined as the application of computer science to analyze biological sequence data (nucleic acid or protein data) (Attwood and Parry-Smith, 1999; Gibas and Jambeck, 2001; Tsai, 2002). The use of computers in the identification of genes and in nucleotide sequence analysis is known as genomics; and their use in protein sequence analysis, alignment, and the prediction of secondary protein structure from amino acid sequences is collectively known as proteomics (Tsai, 2002). Bioinformatics is an indispensable tool for

genome projects, since these projects generate substantial amounts of data unmanageable except with the help of computers.

Chemical biology/biochemistry is a noncomputational continuum of disciplines concerned with the atomic-molecular basis of life, health, disease, and cure. Molecular medicine, gene therapy, and molecular evolution fall into this broad category.

Computational biochemistry promotes the generally qualitative discourse of chemical biology into the quantitative realm. In this chapter, "computational biochemistry" implies "computational chemistry" (see below) applied to biological molecules. The application of computational and theoretical chemistry to biological problems is a well established science reviewed in textbooks dating as early as the 1960s (Carloni and Alber, 2003; Pullman and Pullman, 1963; Richards, 1983), and providing the theme for a series of well known annual symposia published in the International Journal of Quantum Chemistry: Quantum Biology Symposia.

Computational chemistry falls broadly into three subdivisions (Cramer, 2002; Doucet and Weber, 1996; Schlick, 2002): (1) Electronic structure methods (Foresman and Frisch, 1996; Szabo and Ostlund, 1989), which are mainly concerned with solving the time-independent molecular Schrödinger equation, they provide the most detailed description of the geometry, reactivity, and physicochemical properties of biological molecules at the most fundamental level; (2) Molecular modeling or molecular mechanics (Schlick, 2002), in which the biological molecule is treated as a classical collection of point charges linked by springs, and which provide geometries and energies of large biological molecules by solving classical (nonquantum) equations; and (3) Molecular dynamics and Carr-Parinello method, which are concerned with the temporal evolution of the system (Carloni and Alber, 2003; Fraga *et al.*, 1995; Frenkel and Smit, 2002).

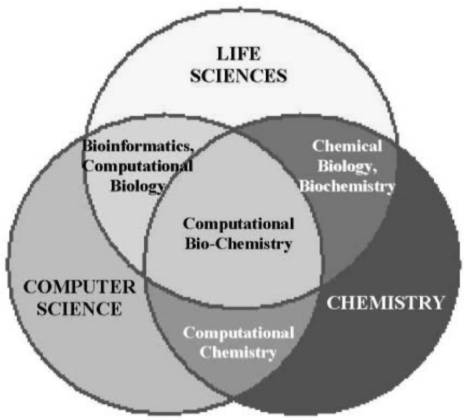

Figure 23.1. A Venn diagram representing the relationship between the life sciences, chemistry and computer science. This chapter focuses on the central region of this diagram, computational biochemistry. (Redrawn with permission–with modification and additions–after Figure. 1.2, p.7 of Tsai, 2002).

Computational biochemistry is a vast field (Náray-Szabó, 1986). This chapter reviews only a small selection of recent examples showing the relevance of computational chemistry to the life sciences. The goal is to give the reader an idea of the kinds of contributions this field has to offer the poor in developing countries.

Contributions of Computational Chemistry

Computational chemistry provides an arsenal of theoretical methods, of increasing level of sophistication, which allows the calculation of the three dimensional geometry of biologically important molecules. This is performed by minimizing the total energy of the molecular system with respect to variations in all the geometric parameters of interest. This procedure is known as "geometry optimization" (Foresman and Frisch, 1996).

The inclusion of solvent effects in geometry optimization enables one to study the conformation of pharmacologically important molecules in their natural (solvated) state as they exist in the aqueous biological milieu (Richards, 1983). This is one of the pillars of modern drug design (Smith, 1988), since it yields the three-dimensional shape of the drug or substrate molecule to which the receptor pocket should exhibit steric and electronic complementarity (Ariëns *et al.*, 1979; Bader *et al.*, 1992). Flexible molecules such as histamine, enkephalins, or acetylcholine can each have more than one receptor, with completely different pharmacological profiles. This is puzzling in the context of the "lock and key" model of drug-receptor complementarity: How can one "key" be complementary in shape to more than one "lock"? The puzzle is quickly resolved upon the realization that these molecules can populate different stable geometrical conformations, each of which exhibiting maximal specificity for one specific complementary receptor (Richards, 1983). This structural knowledge–available from computational chemistry - is crucial for the design of receptor-specific "rigid" analogs. Such analogs are designed by matching and superimposing them to the one conformer that targets specifically the receptor of interest at the exclusion of the other receptors (Richards, 1983).

The development of efficient geometry optimization algorithms and of fast computers coincided also with an unprecedented growth in X-ray diffraction data. X-ray crystallography yields experimental molecular geometries and electron densities of the molecules of interest. Numerous X-ray diffraction geometries of proteins were determined with the substrate molecule bound in the receptor pocket, (RCSB) enabling scientists to study directly the molecular determinants of substrate-protein binding.

Prior to the act of binding, the last step in molecular recognition, a substrate molecule must first approach its receptor in a proper orientation. The approach of a drug molecule to a protein receptor is dictated by the interaction of their respective electron density distributions. The electron density distribution of the protein creates the electrostatic field that interacts with the electron density distribution of the

incoming molecule and directs it along the most favorable path of approach (Náray-Szabó, 1989).

Computational chemistry also allows one to study the geometries of structure that cannot be observed experimentally, such as transition states. By following the reaction paths of biochemical reactions one can gain insight into such phenomena as biological catalysis, mechanisms of radiation damage to DNA, or the mechanisms of action of antitumour drugs (Ban *et al.*, 2001, 2002).

Quantitative structure-activity relationships (QSAR)

QSAR studies are ubiquitous in drug design and in the prediction of the toxicological profile of molecules. This widely used approach uses robust statistics (Mager, 1984) to correlate the biological activity of a series of related compounds to their physicochemical properties (whether these properties are experimentally determined, the result of a quantum chemical calculations, or a combination of both). The basic and simplest underlying assumption of a typical QSAR study may be expressed mathematically:

$$\text{biological activity} \equiv \log\left(\frac{1}{C}\right) = \text{constant} + \sum_{i=1}^{m}\sum_{n} a_{i,n}\ x_i^n$$

where C is the concentration of the compound necessary to elicit a particular biological response (such as LD50, ED50); x_i is the structural, physicochemical, or quantum-chemically-derived property raised to the power n; and $a_{i,n}$ are the weights with which x_i^n enters into the model. Recent successful applications of the QSAR approach are overwhelmingly numerous; a few examples follow.

Vendrame *et al.*, (2002) used the calculated HOMO-LUMO gap (the energy gap between the highest occupied molecular orbitals, HOMO, and the lowest unoccupied molecular orbital, LUMO) and the local density of electronic states (LDOS) to develop a powerful QSAR model predicting the biological activity of steroid with 100% success rate. They also constructed a related QSAR model to identify the carcinogenic activity of a polycyclic aromatic hydrocarbon (PAH), a model that exhibited an accuracy of over 80% (Coluci *et al.*, 2002). A quantum chemical study of 270 nitroaromatic compounds revealed that their electron affinity offers a statistically significant basis for the discrimination between those that are mutagenic (Ames test positive) and those that are not (Ames test negative) (Llorens *et al.*, 2002). Hatch *et al.*, (2001) developed QSAR models for 80 amines with mutagenic activities spanning 10 orders of magnitude based on the total energy of the conjugated B-electrons and on the energy of the LUMO. Each is the single variable with the highest correlation with mutagenic potency.

Quantum Theory of Atoms in Molecules and Life Sciences

Quantum theory was originally developed to yield information on a whole quantum system, such as a molecule, by the action of appropriate operators on *P*. The quantum theory of atoms in molecules (QT-AIM) is a generalization of the quantum theory to subsystems, or "parts" of a quantum system delimited in three-dimensional space (Bader, 1990, 1994; Popelier, 2000). The philosophy behind the theory is that atoms and functional groups retain characteristic signatures in different molecular environments, and hence, should be identifiable within a molecule. The bold conceptual achievement of QT-AIM is the discovery that *P* itself dictates a unique way to partition the electron density of a molecule into its constituent atoms. The relevance of the theory to biology and medicinal chemistry is immediately evident since the QT-AIM enables one to focus only on *a part* of the system–such as a pharmacophore (Bader *et al.*, 2003; Matta, 2003).

Bohórquez *et al.*, (2003) published a study where they used QT-AIM-derived atomic properties in conjunction with powerful statistical techniques to characterize the 20 natural amino acids into chemically related groups. The classification generated by this group emerges naturally from the analysis without interference from the analyst, and yet completely matches the empirical classification. In another study, QT-AIM-derived properties were used to construct several QSAR models capable of accurately predicting a variety of experimental physicochemical and biological properties of the amino acids (r^2 typically greater than 0.95) (Matta and Bader, 2003). The predicted experimental properties include: partial molar volumes; energies of hydration; partition coefficients; changes in protein stability of proteins upon mutation; and the second (middle) letter of the triplet genetic code itself (Matta and Bader, 2003).

Adam (2002) derived thermodynamic relations showing that the pK_a of an acid is approximately proportional to the QT-AIM atomic energy of the acidic hydrogen. He tested his approximation on a large number of organic acids achieving a remarkable agreement with his experiment.

O'Brien and Popelier (2001) define a "bond property space" wherein a given point fixes the values of a chosen set of bonding indices for a given interaction. They then use this space to define a measure of molecular similarity. The method is called quantum topological molecular similarity (QTMS), and is directly applicable to the construction of QSAR models. The method has exceptional promise for drug design by being capable of automatically locating a pharmacophore in a series of related drugs with minimal human interference (O'Brien and Popelier, 1999, 2001; Popelier, 1999).

A challenge: large complex biological molecules and biopolymers

Electronic structure methods scale very rapidly with the size of the system. This nonlinear and very fast scaling presents a major bottleneck limiting the application of computational chemistry to biological molecules, since these molecules tend to be large and complex.

Several methods have been conceived to circumvent this scaling problem with various degrees of success. The divide-and-conquer method was pioneered by Yang (1991a,b, 1992) and Yang and Lee (1995), and the linear scaling approach (Scuseria, 1999), which have been applied to perform calculations on small peptides. Mezey uses "fuzzy density" building blocks to build the electron densities of large molecules (Exner and Mezey, 2003). Song *et al.*, (2002) designed the transferable atom equivalent (TAE) technology. A TAE is a calculated atomic electron densities extracted from molecular moulds according to QT-AIM, and which can be retrieved from a computerized database to be merged on demand with one another. TAE-derived electron density descriptors were used to construct QSAR models capable of accurately predicting protein retention times in anion-exchange chromatography systems. Massa *et al.*, (1995) and Huang *et al.*, (1996) express the density of a large molecule as a sum of densities of fragments. The orbitals of each fragment are used to construct a density matrix, and the sum of the fragment density matrices yield the density matrix for the whole molecule, which is subjected to certain quantum constraints. The fragment matrices can be obtained from either theoretical calculations or from experimental X-ray structure factors. A data bank is being built of transferable multipolar electron density parameters obtained from a fitting of the X-ray structure factors (Pichon-Pesme *et al.*, 1995; Pichon-Pesme *et al.*, 1992; Wiest *et al.*, 1994). Their strategy is to transfer the multipolar charge-density parameters obtained from ultra high resolution X-ray diffraction experiments on amino acids and small peptides to similar atoms in a large protein, significantly improving the refinement statistics and its electron density description (Jelsch *et al.*, 1998). The method was shown to dramatically enhance the resolution of crambin (Jelsch *et al.*, 2000) and scorpion toxin (Housset *et al.*, 2000). Chang and Bader (1992) have shown that the density of a polypeptide can be reconstructed by linking of amino acid residues matched at their amidic zero-flux surfaces that bound and define each amino acid residue. In an extension to this method, Bader and Martin (1998 and Martin (2001) obtained a complete library of accurate densities of tripeptides of the type Gly|Aa|Gly, where Aa stands for any of the 20 genetically encoded amino acid residues and the vertical bars to the zero-flux amidic surfaces bounding the residue within the tripeptide mold. Software was developed to link these amino acids residues densities sequentially in an arbitrary order and thus obtain an excellent approximation to the density of a peptide of arbitrary length in seconds (Martín, 2001). Matta (2001) used a related method, the buffered fragment method, to reconstruct accurately the physicochemical properties of large and complex opioid molecules from small fragments.

None of these methods is perfect, and each has its advantages and limitations. The continual improvement of these slow-scaling methods, coupled with the explosive growth in computer speed, will enable chemists one day to perform full-fledged *ab initio* quantum mechanical calculation on a whole protein. Such a calculation on even a water molecule was nearly impossible a few decades ago.

Computational Chemistry and the Poor

Computational chemistry has become an indispensable tool for drug design and, in this way, can contribute directly to the well being of the poor. This is particularly true if the power of computational chemistry is exploited to aid in the discovery of more effective drugs for diseases endemic in the poorer countries and communities: malaria, tuberculosis, schistosomiasis, leprosy, and AIDS. Of the diseases of the poor, only a few, such as AIDS, also represent a public health risk to the rich. The rich are typically insufficiently alarmed by the diseases that are exclusively of the poor to consider them as high research priorities. It is therefore the task of the poor to take the lead in solving their own problems.

Universities and other research institutions in the developing countries are particularly encouraged to invest in computer applications in biology, the fields represented by the intersections of the circles in Figure 23.1. Plagued by extremely thin funding, science education and research in the developing countries have no choice but to rely on low-cost experimentation in the life sciences (Ali, 1989). Computational biochemistry is among the least costly disciplines. For example a state-of-the-art quantum chemical calculation can be performed on a US$3000 personal computer using free quantum chemistry code (Schmidt *et al.*, 1993). In contrast, and also as an example, an advanced nuclear magnetic resonance (NMR) spectrometer may cost between US$1 and 5 million. Thus, computational and biotheoretical chemistry are fields of research to which developing countries can, and should, contribute on an equal footing with industrial countries.

The establishment of schools of computational chemistry in developing countries should be seen within the wider context of achieving educational and academic reforms and the pursuit of excellence in these countries. The design of drugs for diseases endemic to the developing countries can be part of the mission of such specialized centers. The transfer of this technology between the developing and industrial countries is something that should be strongly encouraged and funded.

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University are thanked for their critical reading of the manuscript. Wiley-Liss Publishers are thanked for their permission to redraw (with modification) Figure 23.1.

References

Adam, K.R. 2002. New density functional and atoms in molecules method of computing relative pKa values in solution. J. Phys. Chem. A. 106: 11963-11972.

Ali, F.M. 1989. Proceedings: First International Conference on Low Cost Experiments in Biophysics. Cairo: Cairo University.

Ariëns, E.J., A.J. Beld, J.F. Rodrigues de Miranda, and A.M. Simonis. 1979. The pharmacon-receptor-effector concept. In: O'Brien, R.D. (ed.). The Receptors: A Comprehensive Treatise, (Vol.1: General Principles and Procedures). New York: Plenum Press, p.33-91.

Attwood, T.K., and D.J. Parry-Smith. 1999. Introduction to Bioinformatics. London: Prentice Hall.

Bader, R.F.W. 1990. Atoms in Molecules: A Quantum Theory. Oxford, U.K.: Oxford University Press.

Bader, R.F.W. 1994. Principle of stationary action and the definition of a proper open system. Phys. Rev. B 49: 13348-13356.

Bader, R.F.W., and F.J. Martín. 1998. Interdeterminancy of basin and surface properties of an open system. Can. J. Chem. 76: 284-291.

Bader, R.F.W., C.F. Matta, and F.J. Martín. 2003. Atoms in medicinal chemistry. In: Alber, F., and P. Carloni (eds.). Medicinal Quantum Chemistry. Weinheim: Wiley-VCH, p.201-231.

Bader, R.F.W., P.L.A. Popelier, and C. Chang. 1992. Similarity and complementarity in chemistry. J. Mol. Struct. (Theochem) 255: 145-171.

Ban, F.Q., J.W. Gauld, and R.J. Boyd. 2001. Modeling the action of an antitumor drug: A density functional theory study of the mechanism of tirapazamine. J. Am. Chem. Soc. 123: 7320-7325.

Ban, F.Q., K.N. Rankin, J.W. Gauld, and R.J. Boyd. 2002. Recent applications of density functional theory calculations to biomolecules. Theor. Chem. Acc. 108: 1-11.

Bohórquez, H.J., M. Obregón, C. Cárdenas, E. Llanos, C. Suárez, J.L. Villaveces, and M.E Patarroyo. 2003. Electronic energy and multipolar moments characterize amino acid side chains into chemically related groups. J. Phys. Chem. A. 107: 10090-10097.

Carloni, P., and F.E. Alber. 2003. Quantum Medicinal Chemistry. Weinheim: Wiley-VCH.

Chang, C., and R.F.W. Bader. 1992. Theoretical construction of a polypeptide. J. Phys. Chem. 96: 1654-1662.

Coluci, V.R., R. Vendrame, R.S. Braga., and D.S. Galvão. 2002. Identifying relevant molecular descriptors related to carcinogenic activity of polycyclic aromatic hydrocarbons (PAHs) using pattern recognition methods. J. Chem. Inf. Comput. Sci. 42: 1479-1489.

Cramer, C.J. 2002. Essentials of Computational Chemistry: Theories and Models. New York: John Wiley & Sons Ltd.

Dirac, P.A.M. 1929. Quantum mechanics of many-electron systems. Proc. Roy. Soc., Ser. A 123: 714-733.

Doucet, J.-P., and J. Weber. 1996. Computer-Aided Molecular Design: Theory and Applications. London: Academic Press Ltd.

Exner, T.E., and P.G. Mezey. 2003. Ab initio quality properties for macromolecules using ADMA approach. J. Comput. Chem. 24: 1980-1986.

Foresman, J.B., and A. Frisch. 1996. Exploring Chemistry with Electronic Structure Methods, (Second Edition). Pittsburgh: Gaussian, Inc.

Fraga, S., J.M.R. Parker, and J.M. Pocock. 1995. Computer Simulations of Protein Structures and Interactions. Berlin: Springer.

Frenkel, D., and B. Smit. 2002. Understanding Molecular Simulation: From Algorithms to Applications. New York: Academic Press.

Gay-Lussac, J.L. 1808. Memoire de la Societe D'Arcuiel 2: 207.

Gibas, C., and P. Jambeck. 2001. Developing Bioinformatics Computer Skills. Cambridge: O'Reilly.

Hatch, F.T., M.G. Kinze, and M.E. Colvin. 2001. Extended quantitative structure-activity relationships for 80 aromatic and hetrerocyclic amines: Structural, electronic, and hydropathic factors affecting mutagenic potency. Environ. Mo . Mutagen. 38: 268-291.

Housset, D., F. Benabicha, V. Pichon-Pesme, C. Jelsch, A. Maierhofer, S. David, J.C. Fontecilla-Camps, and C. Lecomte. 2000. Towards the charge-density study of proteins: A room-temperature scorpion-toxin structure at 0.96Å resolution as a first test case. Acta Cryst. D56: 151-160.

Huang, L., L. Massa, and J. Karle. 1996. Kernel projector matrices for Leu1-zervamicin. Int. J. Quantum. Chem: Quantum Chem. Symp. 30: 479-488.

Jelsch, C., V. Pichon-Pesme, C. Lecomte, and A. Aubry. 1998. Transferability of multiple charge-density parameters: Application to very high resolution oligopeptide and protein structures. Acta Cryst. D54: 1306-1318.

Jelsch, C., M.M. Teeter, V. Lamzin, V. Pichon-Pesme, R.H. Blessing, and C. Lecomte. 2000. Accurate protein crystallography at ultra-high resolution: Valence electron distribution in crambin. Proc. Natl. Acad. Sci. USA 97: 3171-3176.

Krogh-Jespersen, K. 2004. Introduction to Computational Chemistry. New Brunswick, NJ (USA): Dept. of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey.

Llorens, O., J.J. Perez, and H.O.Villar. 2002. Investigation of structural and electronic biases in mutagenic compounds. Int. J. Quantum Chem. 88: 107-117.

Mager, P.P. 1984. Multidimensional Pharmacochemistry: Design of Safer Drugs. London: Academic Press Inc.

Martín, F.J. 2001. Theoretical Synthesis of Macromolecules from Transferable Functional Groups. Ph.D. Thesis. Hamilton: McMaster University.

Massa, L., L. Huang, and J. Karle. 1995. Quantum crystallography and the use of kernel projector matrices. Int. J. Quantum. Chem: Quantum Chem. Symp. 29: 371-384.

Matta, C.F. 2001. Theoretical reconstruction of the electron density of large molecules from fragments determined as proper open quantum systems: the properties of the oripavine PEO, enkephalins, and morphine. J. Phys. Chem. A 105: 11088-11101.

Matta, C.F. 2003. Application of the quantum theory of atoms in molecules to selected physicochemical and biophysical problems: focus on correlation with experiment. J. Comput. Chem. 24: 453-462.

Matta, C.F., and R.F.W. Bader. 2003. Atoms-in-molecules study of the genetically-encoded amino acids. III. Bond and atomic properties and their correlations with experiment including mutation-induced changes in protein stability and genetic coding. Proteins: Struct. Funct. Genet. 52: 360-399.

Náray-Szabó, G. 1986. Theoretical Chemistry of Biological Systems. New York: Elsevier.

Náray-Szabó, G. 1989. Electrostatics in computer-aided drug design. Int. J. Quantum Chem.Quantum Biol.Symp. 16: 87-99.

O'Brien, S.E., and P.L.A. Popelier. 1999. Quantum molecular similarity. Part 2: the relation between properties in BCP space and bond length. Can. J. Chem. 77: 28-36.

O'Brien, S.E., and P.L.A. Popelier. 2001. Quantum molecular similarity. 3. QTMS descriptors. J. Chem. Inf. Comput. Sci. 41: 764-775.

Pichon-Pesme, V., C. Lecomte, and H. Lachekar. 1995. On building a data bank of transferable experimental density parameters: Application to polypeptides. J. Phys. Chem. 99: 6242-6250.

Pichon-Pesme, V., C. Lecomte, R. Wiest, and M. Bénard. 1992. Modeling fragments for the ab initio determination of electron density in polypeptides. An experimental and theoretical approach to the electron distribution in Leu-enkephalin trihydrate. J. Am. Chem. Soc. 114: 2713-2715.

Popelier, P.L.A. 1999. Quantum Molecular Similarity. 1. BCP space. J. Phys. Chem. A 103: 2883-2890.

Popelier, P.L.A. 2000. Atoms in Molecules: An Introduction. London: Prentice Hall.

Pullman, B., and A. Pullman. 1963. Quantum Biochemistry. New York: Interscience Publishers.

RCSB. Protein Data Bank (PDB).

Richards, W.G. 1983. Quantum Pharmacology, (second edition). London: Butterworth & Co., Ltd.

Schlick, T. 2002. Molecular Modeling and Simulation: An Interdisciplinary Guide. New York: Springer.

Schmidt, M.W., K.K. Baldridge, J.A. Boatz, S.T. Elbert, M.S. Gordon, J.H. Jensen, S. Koseki, N. Matsunaga, K.A. Nguyen, S.J. Su, T.L. Windus, M. Dupuis, and J.A. Montgomery. 1993. General atomic and molecular electronic-structure system (GAMESS). J. Comput. Chem. 14: 1347-1363.

Schrödinger, E. 1944. What is Life? Cambridge: Cambridge University Press.

Scuseria, G.E. 1999. Linear scaling density functional calculations with gaussian orbitals. J. Phys. Chem. A 103: 4782-4790.

Smith, H.J. 1988. Smith and Williams' Introduction to the Principles of Drug Design, Second Ed. London: Wright.

Song, M., C.M. Breneman, J. Bi, N. Sukumar, K.P. Bennett, S. Cramer, and N. Tugcu. 2002. Prediction of protein retention times in anion-exchange chromatography systems using support vector regression. J. Chem. Inf. Comput. Sci. 42: 1347-1357.

Szabo, A., and N.S. Ostlund. 1989. Modern Quantum Chemistry: Introduction to Advanced Electronic Structure Theory. New York: Dover Publications, Inc.

Tsai, C.S. 2002. An Introduction to Computational Biochemistry. New York: Wiley-Liss, Inc.

Vendrame, R., V. R. Coluci, R.S. Braga, and D.S. Galvão. 2002. Structure-activity relationship (SAR) studies of the tripos benchmark steroids. J. Mol. Struct. (Theochem) 619: 195-205.

Wiest, R., V. Pichon-Pesme, M. Bénard, and C. Lecomte. 1994. Electron distributions in peptides and related molecules. Experimental and theoretical study of Leu-enkephalin trihydrate. J. Phys. Chem. 98: 1351-1362.

Yang, W. 1991a. Direct calculation of electron density in density-functional theory. Phys. Rev. Lett. 66: 1438-1441.

Yang, W. 1991b. Direct calculation of the electron density in density-functional theory: Implementation for benzene and a tetrapeptide. Phys. Rev. A 44: 7823-7826.

Yang, W. 1992. Electron density as the basic variable: A divide-and-conquer approach to the ab initio computation of large molecules. J. Mol. Struct. (Theochem) 255: 461-479.

Yang, W., and T.-S. Lee. 1995. A density-matrix divide-and-conquer approach for the electronic structure calculations of large molecules. J. Chem. Phys. 103: 5674-5678.

Chapter 24

Impact of Chemical and Screening Technologies in Drug Discovery

Magid Abou-Gharbia

Introduction

The pharmaceutical industry has witnessed intense pressure and fierce competition during the last decade. Major challenges facing the industry include the increase in the complexity of NCEs (new chemical entities), the increase in regulatory requirements, patent expiration of top products, and increase in generic competition. Nevertheless, pharmaceutical companies are continuing to race and jockey for position to capture a large portion of the global pharmaceutical market, which is growing steadily and is projected to exceed US$550 billion by 2010. Many research organizations have adopted several approaches to ensure survival and domination. Improving productivity through innovation and discovery of novel drug candidates is the cornerstone of this strategy.

Drug discovery and development is a challenging and complex process that involves the dedicated multidisciplinary efforts of many R&D functions. Breakthroughs in innovation and process refinements have dominated drug discovery during the last decade, which have been aimed at increasing efficiencies and, thus, reducing cycle time. Despite these technological advances, the number of NCEs and new biological entities (NBEs) approved for human use has declined in recent years; only 25 new drugs were introduced across the industry in 2001, the least productive of the past decade (Graul, 1999; Bernardelli *et al.*, 2002). The recent deciphering of the human genome led to an explosion in genomic technologies and, subsequently, tremendous progress toward identifying and sequencing human genes, resulting in a significant increase in the number of potential drug targets. Meeting these demands will require a well-integrated discovery effort, and the application of many state-of-the-art technological and developmental capabilities at the earlier stages of the R&D process, to increase the "hit rate" for identifying clinical candidates that reach new drug application (NDA) registration.

Chemical and Screening Technologies

Chemical and Screening technologies play a critical role in impacting all phases of drug discovery pre-exploratory functions, through the exploratory, discovery phases of projects, and selection of optimized compounds to advance to the development phase (Figure 24.1). In recent years several state-of-the-art technologies were introduced throughout the discovery phases to increase effectiveness and advance compounds in a timely fashion. Well-known examples include high throughput screening (HTS), combinatorial chemistry, computer aided drug design (CADD), and high throughput physicochemical profiling methods. The ability to rapidly identify, evaluate, and screen human targets is critical for the success of drug discovery efforts.

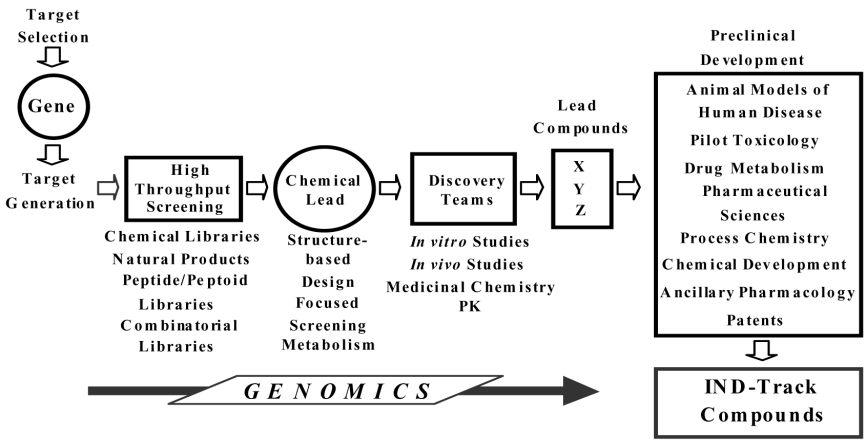

Figure 24.1. Drug discovery process.

Discovery of Novel Drug Candidates

Several successful medicinal chemistry approaches have been used successfully to optimize initial lead "hits" identified via screening natural products from microbial and botanical extracts, compound libraries, rational and/or structure-based drug design (Ashton *et al.*, 1996a, 1996b; Hughes, 1996). This report highlights some of our available technologies and approaches that were used successfully in optimizing early leads into drug candidates. To that end modification of natural products calicheamicin and rapamycin provided the anticancer agents Mylotarg‘ and CCI-779, respectively, and rational receptor/ligand-based drug design led to the discovery of the antidepressant Effexor®.

Mylotarg™

Mylotarg™ (Figure 24.2) represents a first-in-class antibody-targeted chemotherapeutic agent, the first true "silver bullet" anticancer drug. It is the optimized antibody conjugate containing engineered human CD33 antibody attached via a bifunctional linker to the cytotoxic agent, calicheamicin (Lee *et al.*, 1987a, 1987b). The antibody targets the DC33 antigen commonly found on the surface of acute myelogenous leukemia (AML) cells. The resulting calicheamcin conjugate (Hinman *et al.*, 1993)/CD33 complex then becomes internalized. Once inside the cell, the calicheamicin is released through hydrolytic cleavage by acidic lysosomes and migrates, at least in part, to the nucleus. Calicheamicin binds to the DNA minor groove causing double-stranded DNA breaks and, ultimately, cell death. Mylotarg™ was successfully marketed in 2000 as an effective anti-tumor agent for the treatment of AML.

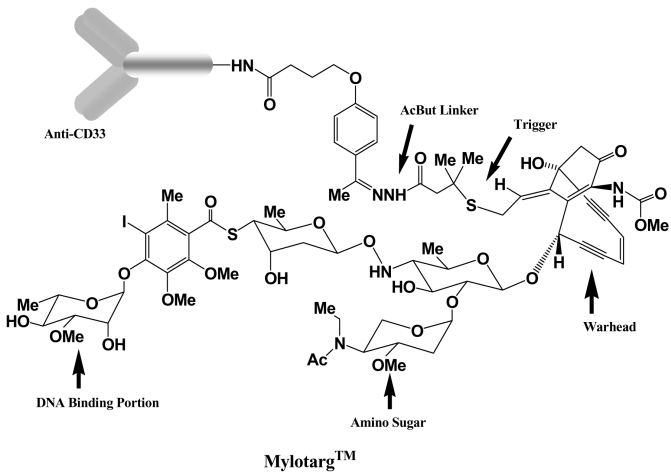

Figure 24.2. Calicheamicin conjugates.

Temsirolimus (CCI-779)

Rapamycin is a novel immunosuppressant natural product with unique mechanisms of action (Sehgal *et al.*, 1994; Molnar-Kimber, 1996). It binds to FKBP and forms a complex that binds with m-TOR (mammalian target of rapamycin) and inhibits cell cycle progression. Rapamycin was marketed in 1999 as Rapamune® for the treatment of transplantation rejection, and is regarded as the fastest growing immunosuppressant for renal transplantation. Medicinal chemistry manipulation of the rapamycin functionalities led to the synthesis of several novel rapamycin derivatives. Over 700 rapamycin derivatives were synthesized and evaluated for their

potential biological activity. The hindered ester (Cell Cycle Inhibitor; CCI-779) was selected and subjected to further preclinical and clinical evaluations; it is currently in Phase III as an anti-cancer agent (Gibbons *et al.*, 1999; Yu *et al.*, 2001a, 2001b; Skotnicki *et al.*, 2001) and is also being evaluated for its potential therapeutic utility in rheumatoid arthritis and multiple sclerosis (Phase II) (Figure 24.3).

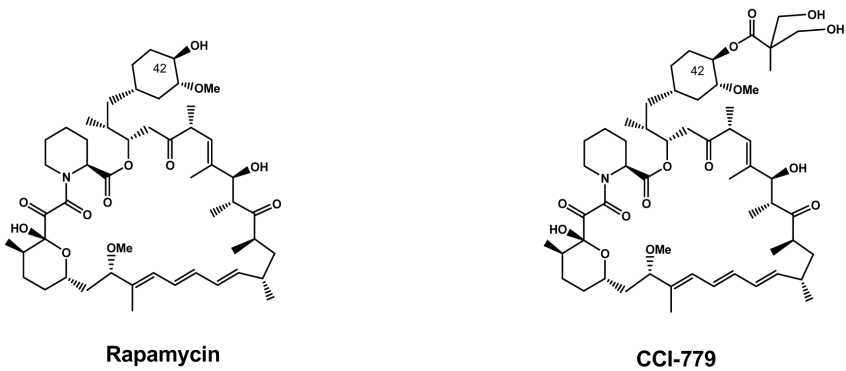

Figure 24.3. Rapamycin and CCI-779.

Effexor®

Multidimensional lead optimization utilizing the receptor/ligand-based design approach is usually applied in neuroscience research where structural information of biological targets is not available. Efforts in neuropsychiatric areas led to the discovery of a number of selective norepinephrine re-uptake inhibitors (SNRIs), one of which, Effexor“ (Figure 24.4), is currently marketed as an effective antidepressant agent (Yardley *et al.*, 1990).

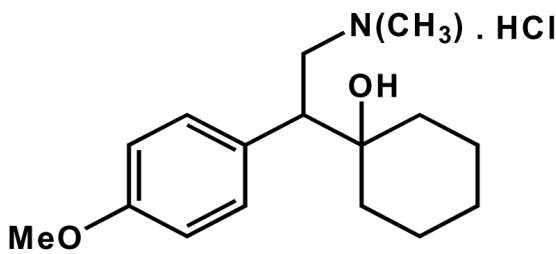

Figure 24.4. Effexor®.

Challenges Facing Drug Discovery and Development

The various challenges facing drug discovery and development are shown in Figure 24.5.

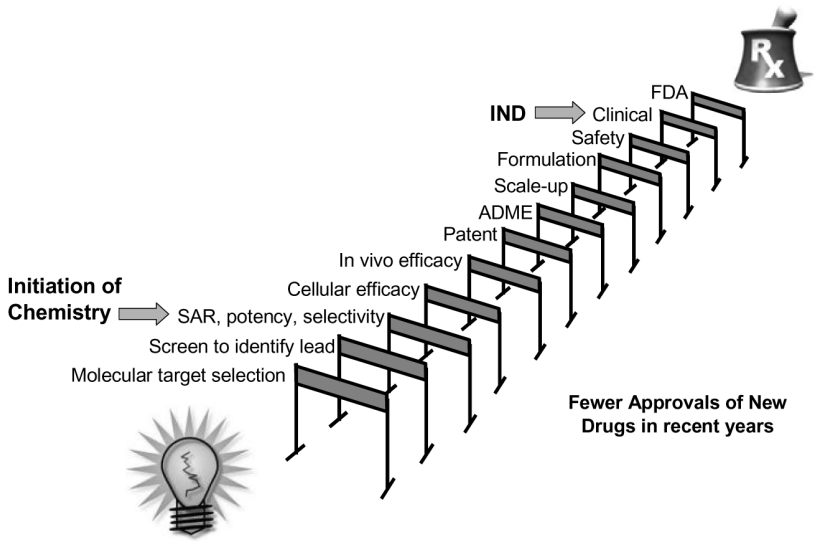

Figure 24.5. Challenges facing drug discovery and development from concept to pharmacy.

Less than 10% of the new molecular entities (NMEs) that enter clinical trials in Phase I will make it to market and become available to patients (M. Wentland, 2000 pers. comm.). Despite the many challenges facing the pharmaceutical industry, many companies are successful in discovering and developing and marketing innovative drugs. For example, Wyeth Pharmaceutical is one of the leading few pharmaceutical companies that successfully introduced over the years novel therapies in three platforms (Figure 24.6):

- Small molecule therapeutics, such as Rapamune®, Effexor®, Protonix®, are already marketed drugs and three new chemical entities (NCEs), Temsirolimus, Tagycil and Bazedoxifene will be launched during 2005-2007.
- Protein therapeutics such as Mylotarg™, Enbrel®, and ReFacto®.
- Vaccine therapeutics such as Prevnar®, combating pneumococcal infection, and Meningitec™.

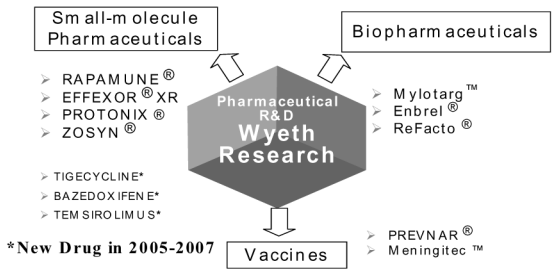

Figure 24.6. High impact medicines in three platforms.

Developing Countries and the Pharmaceutical Industry

Despite these advances and breakthroughs in health care, when it comes to the topic of the pharmaceutical industry and the ongoing efforts by the "multinationals," developing countries see clear division for the world market of pharmaceuticals, with products being developed for industrial countries driven by a high profit margin, leaving developing countries in dire need of basic health care. The reality is that the pharmaceutical industry, the "multinationals," is a research-based enterprise with strong commitment to innovation and expensive R&D investment. Pharmaceutical industry efforts are focused on the discovery of new therapies for unmet medical needs, such as Alzheimer's disease, infectious diseases, multiple sclerosis, and many other debilitating diseases. These diseases are not only affecting the industrial countries, but are also prevalent throughout the world, affecting the rich and the poor. The pharmaceutical industry supports improving access to existing and future innovative medicines, through collaborative efforts with developing country governments and health organizations such as WHO. This includes donating assistance, medicines, funds for infrastructure development, and expertise. In addition, collaboration and partnership of developing countries and the pharmaceutical industry helps to ensure the development of effective cures for diseases specific to those countries.

With the advance in genotyping, conducting clinical trials in these countries will facilitate the development of new therapies against particular disease genotypes. For example, hepatitis genotype 4 is most common in Africa, whereas hepatitis genotype 1 and genotype 2 are most common in the USA and Europe. Collaboration in this area will facilitate the development of effective antiviral agents against genotype 4. Developing countries have the needed talent and resources in their academic and research institutions that could be directed toward initiating early phases of drug discovery, particularly lead identification and lead optimization as shown in Figure 24.1. Initiating pharmaceutical research in these countries will help in creating

opportunities for partnerships with multinationals at the later stages of R&D. Taking these steps will create the proper environment to encourage practicing patent protection and commitment for intellectual property protection, and will ultimately lead to stimulating investment in these countries and ensuring access to current and future innovative medicines.

Acknowledgments

I am indebted to many Wyeth researchers who are responsible for the discovery of these three breakthroughs, first-in-class drug candidates. Sincere thanks to my colleagues, Guy Carter, George Ellestad, Hassan Elokdah, Phil Hamann, Boyd Harrison, Jerry Skotnicki, P.-E. Sum, and Janis Upeslacis for providing constructive feedback and suggestions on the content of the presentation. I extend sincere thanks to Ms. Marie Arcaro for her tireless efforts during the preparation of the presentation and the manuscript.

References

Ashton, M.J., M.C. Jaye, and J.S. Mason. 1996a. New perspectives in lead generation I: Discovery of biological targets. Drug Discovery Today 1:11-15.

Ashton, M.J., M.C. Jaye, and J.S. Mason. 1996b. New perspectives in lead generation I: Discovery of biological targets. Drug Discovery Today 1:71-78.

Bernardelli, P., B. Gaudillière, and F. Vergne. 2002. Trends and perspectives: To market, to market–2001. In: Doherty, A.M. (ed), Annual Reports in Medicinal Chemistry Volume 37. Academic Press, San Diego, pp. 257-277.

Gibbons Jr., J.J., C. Discafani, R.R. Petersen, R. Hernandez, J.S. Skotnicki, and P. Frost. 1999. The effect of CCI-779, a novel macrolide anti-tumor agent, on the growth of human tumor cells in vitro and in nude mouse xenographs in vivo. Proceedings of the American Association for Cancer Research 40: Abstr. 2000.

Graul, A.I. 1999. The Year's New Drugs: A historical and research perspective on the 46 new products that reached their first markets in 1998. Drug News Perspectives 12:27-43.

Hinman, L.M., P.R. Hamann, A.T. Menendez, R. Wallace, F.E. Durr, and J. Upeslacis. 1993. Preparation and characterization of monoclonal antibody conjugates of the calicheamicins: A novel and potent family of antitumor antibiotics. Cancer Research 53:3336-3342.

Hughes, D. 1996. Drug Discovery Today and the status quo. Drug Discovery Today 1:1.

Lee, M.D., T.S. Dunne, M.M. Siegel, C.C. Chang, G.A. Ellestad, G.O. Morton, W.J. McGahren, and D.B. Borders. 1987a. Calichemicins, a novel family of antitumor antibiotics. 2. Chemistry and partial structure of calichemicin g1 I. Journal of the American Chemical Society 109: 3466-3468.

Lee, M.D., T.S. Dunne, M.M. Siegel, C.C. Chang, G.O. Morton, and D.B. Borders. 1987b. Calichemicins, a novel family of antitumor antibiotics. 2. Chemistry and structure of calichemicin g1 I. Journal of the American Chemical Society 109: 3464-3466.

Molnar-Kimber, K.L. 1996. Mechanism of Action of Rapamycin (Sirolimus, Rapamune). Transplantation Proceedings 28: 964-969.

Sehgal, S.N., K.L. Molnar-Kimber, T.D. Ocain, and B.M. Weichman. 1994. Rapamycin: A Novel Immunosuppressive Macrolide. Medicinal Research Reviews 14: 1-22.

Skotnicki, J.S., C.L. Leone, A.L. Smith, Y.L. Palmer, K. Yu, C.M. Discafani, J.J. Gibbons Jr., P. Frost, and M.A. Abou-Gharbia. 2001. Design, Synthesis and Biological Evaluation C-42 Hydroxyesters of Rapamycin: The Identification of CCI-779. Clinical Cancer Research 7:3749s; Proceedings of AACR-NCI-EORTC International Conference Abstract 477.

Yardley, P.J., G.E.M. Husbands, G. Stack, J. Butch, J. Bicksler, J.A. Moyer, E.A. Muth, T. Andree, H. Fletcher III, M.N.G. James, and A.R. Sielecki. 1990. 2-Phenyl-2-(1-hyroxycycloalkyl) ethylamine derivatives: Synthesis and antidepressant activity. Journal of Medicinal Chemistry 33:2899-2905.

Yu, K., L. Toral-Barza, C. Discafani, W.G. Zhang, J.S. Skotnicki, P. Frost, and J.J. Gibbons Jr. 2001a. mTOR, a novel target in breast cancer: the effect of CCI-779, an mTOR inhibitor, in preclinical models of breast cancer. Endocrine-Related Cancer 8: 249-258.

Yu, K., W.G. Zhang, J. Lucas, L. Toral-Barza, R. Petersen, J.S. Skotnicki, P. Frost, J.J. Gibbons. 2001b. Deregulated P13K/AKT/TOR pathway in PTEN-deficient tumor cells correlates with an increased growth inhibition sensitivity to a TOR kinase inhibitor CCI-779. Proceedings of the American Association for Cancer Research 42: Abstr. 4305.

Chapter 25

Losing Life to Cancer: From Science to Ethics

Claude Jasmin

Introduction

The World Health Organization (WHO) estimates that there are over 10 million new cases and 6 million deaths per year, worldwide, due to cancer. In 2020, a 50% increase in incidence is expected, including a 29% rise in developing countries. In the industrial countries, with their ageing populations and heavy exposure to tobacco, cancer is the second leading cause of death (about 25% of the total).

Cancer is most frequent and lethal in people older than 60. Therefore, it is not surprising that in developing countries where the average life expectancy is still far from that of industrial countries, cancer is currently responsible for only 5% of deaths. Poverty, violence, malnutrition, and infectious diseases are the major health burdens in children and young adults in these countries.

However, as the increased longevity of the economically developed countries begins to spread to the rest of the world, WHO projections indicate that nearly two-thirds of the over 300 million new cases of cancer worldwide will strike the populations of developing countries, where deaths due to cancer will double in the next 25 years (Merson, 1992). In 2020, the burden of cancers linked to abuse of tobacco, malnutrition, and infectious agents is expected to be at its peak in developing countries.

Tobacco alone will be responsible for 1 million deaths annually worldwide. In industrial countries, the incidence of tobacco-associated cancers will continue to increase for a period of time, in spite of the current decline in tobacco consumption. This is because cancers linked to tobacco are regularly diagnosed after many years of abuse, and even in individuals who have long since stopped smoking. However, after this period, the incidence of tobacco-associated cancers will fall. Conversely, in the absence of appropriate preventive measures, deaths due to smoking will continue to increase in developing countries.

Inadequate nutrition accounts for 20-30% of certain cancers. The increasing numbers of overweight children in the world is alarming for their future. In the United States, 60% of adults are overweight or obese. Obesity plays a significant role in about 14% of deaths from cancer in American men, and 20% in American women. Indeed, obesity is linked to an increase in breast, liver, colon, rectum, biliary bladder, uterus, ovary, prostate, esophagus, kidney, and pancreas cancers. Obesity is also associated with an increased incidence in myelomas and lymphomas. It is noteworthy that the poor and less well educated are disproportionately more affected. Poverty is an important co-factor. In certain countries, specific nutritional factors are linked to the development of some cancers. For example, aflatoxin is a substance produced by fungi that proliferate and contaminate inappropriately stored peanuts. Aflatoxin is associated with the high incidence of liver cancer reported in some African and Asian countries. In Iran and Japan, smoked foods can be heavily contaminated by carcinogenic substances responsible for cancers of the digestive tract.

In some countries, cancer is linked to a double carcinogenic stimulus. For example, hepatocarcinoma, a cancer arising in the liver, is frequently found in some African and Asian regions where individuals are contaminated by B and C strains of hepatitis viruses able to induce chronic hepatitis and/or cirrhosis. If the patient is also exposed to dietary carcinogens such as the aflatoxin contained in contaminated peanuts, the risk of liver cancer will be significantly increased. Kensler *et al.,* (2003) estimate that an average 30-year interval is needed between the first carcinogenic exposure and the development of cancer. It would be possible to decrease the incidence of liver cancer in these regions by vaccinating against hepatitis viruses, and improving storage conditions of peanuts to eliminate aflatoxin contamination.

Viruses are also a major cause of cancer in both industrial and developing countries. Almost all cancers of the cervix are linked to sexually transmitted papillomavirus infections. Tobacco is an aggravating co-factor.

HIV infection is also linked to increased incidence of lymphoma and Kaposi sarcoma in AIDS patients. In Africa, 90% of HIV-positive patients have no access to health care and standard treatments. Life expectancy in Africa has fallen by 10 years since the beginning of the AIDS epidemic.

Conclusion

This brief overview of the avoidable cancers in industrial and developing countries gives food for thought on issues related to Equity in Cancer and Health:

- Health prevention is a major issue and the responsibility of all governments. Too many lives are being lost in the economically developed and developing countries because appropriate and available policies for prevention have not been implemented. The spread of many debilitating diseases to the individual and to society could be contained through effective education, for example concerning sexually transmitted viral infections such as hepatitis, AIDS, and papilloma viruses linked to cervical cancer. Education on nutrition is also important in all countries, although the issues specific to each need to be addressed differently. AIDS is killing Africa; information on the danger of smoking could save many of the remaining African lives.
- The remarkable gain in longevity in the 20th century, one year of life every four years (25 added years in industrial countries,) has demonstrated the link between health and wealth. Health is a political issue. Healthy societies can only grow with healthy populations.
- A healthy world is in part dependent on our ability to put modern technology to the service of developing countries. This is not only an ethical responsibility but also a question of overall survival.
- Health is not a gift but something to be achieved together.

References

Merson, M.H. 1992. AIDS, cancer and the developing world. In Claude Jasmin and Gabriel Bez (eds.) Cancer, AIDS and Society. International Council for Global Health Progress, p. 17-21.

Kensler, T.W., G.S. Quan, J.G. Chen, and J.D. Groopman. 2003. Translational strategies for cancer prevention in liver. Nature Rev. Cancer, 3: 321-329.

Chapter 26

Female and Male Human Brains: Different, but Complementary, in Intellectual Profile

Annica Dahlström

Introduction

The human brain is the basis for our identity and for all our activities. It can be said: You are your brain, your brain is you. It is the most sophisticated, complicated structure known. About 50 x 1012 nerve cells and 5-6 times as many glia cells work together in an intricate morphologial and chemical network. The nerve cells communicate with chemical substances, transmitters, of which we have identified about 50; but the number is growing each year. Nerve cells have extraordinary anatomical features; each nerve cell receives input to its dendritic tree from 1,000 to10,000 other nerve cells, and, with its axon and the distal branchings, it can, in turn, communicate with thousands of other nerve cells.

The numerous transmitters, the actors of brain activity, can be put in four groups: The *first group*, called "classical transmitters," include well-known small transmitters such as noradrenaline, dopamine, acetylcholine, and serotonin. The *second group* is a large number of small proteins, peptides, composed of 2-≈ 300 amino acids. The *third group* is single amino acids, for example glycine, GABA, taurine, which are found in most of the brain synapses (communication stations). The *fourth group*, the most recently demonstrated, is gases, NO and probably CO, which participate in regulation and communication in the nervous system.

All these transmitter molecules, big and small, can be viewed as "keys" that must fit exactly in a "keyhole," a receptor molecule inserted in the nerve cell membrane, to induce an effect. We know that most transmitters (keys) couple into at least 2-4 different keyholes, inducing different actions in the receiving cell. Serotonin, however, is a remarkable exception, since this single transmitter activates at least 14 different receptors (keyholes). We can assume, therefore, that this transmitter has a vital and global function in the brain. It is here where we see one of the biochemical differences between most men and most women; women on average

appear to use approximately 20% more serotonin (5-HT) than men (Nishizawa *et al.*, 1997), and they have a generally higher density of one of the 14 receptors, the 5-HT1a receptor. A number of studies show that 5-HT is indeed vital for life; low levels of serotonin in the brain are linked with depression, and in suicide cases the level approaches zero (Åsberg, *et al.*, 1976a, b; van Praag, and de Haan 1980).

The phylogenetically "old brain," including the hypothalamus, is the location of all automatic functions of the brain, where survival, food intake, and reproductive functions are based, in humans and other mammals. We have, as humans, been blessed with a very large "new" brain, the two brain halves or hemispheres. They are covered by a 3-4 mm thick layer of "gray substance," containing nerve cell bodies with their receiving and projecting thin ramifications (dendrites and nerve terminal synapses or "contact stations"). This is the base for all our conscious thinking, planning, learning, cultural activities, education, adaptation to society, religious experiences, etc. In the adult, the two hemispheres are diversified as to functions: one, in most cases the left half, is dealing with logical processes, while the other is dealing with emotional experiences. The two halves of the new brain are connected via the corpus callosum, where a great number of nerve fibers (axons) pass from one side to the other.

Gender Differences in Brain Development

The development in an individual is a complicated process, where hormones regulate the processes initiated by different genes. Brain development is basically different in males and females, following two separate patterns or "blueprints." Although in most respects the genders have similar brains, some important differences in the "wiring" of brain connections have been demonstrated.

The male brain is actively masculinized during two periods. The *first period* is during the middle three months of pregnancy. During this period the fetus's testicles have started producing testosterone, which passes into the body and also into the brain, starting the programming toward a male pattern. The *second period* is the first few weeks after the birth of the boy, and it is again his testicles that produce the hormone. So, in the human male there are two time slots required to instruct the growing brain how to react as an adult, in response to testosterone surges (LeVey, 1994; Gorski, 2002).

If the fetus is a girl (XX), she can be masculinized, from a little to a considerable extent, by testosterone from her mother's circulation. In the case of a suprarenal cortical testosterone-producing tumor in the mother, high levels of the hormone can pass the placenta, since testosterone is comparatively free in the blood. Estrogen, on the other hand, is bound to a large protein, alpha-fetoprotein, which prevents the crossing of the placental barrier. Sometimes children are born with the "adrenogenital syndrome," genotype girls who were exposed in utero to high levels of male hormones. It has been shown in female monkeys, as well as in women, that

long-term chronic stress may induce a higher production than normal of testosterone, from the adrenals and from the ovaries of the pregnant female. The effect of testosterone is dose-dependent; the more of the male hormone the more masculine brains (Meisel and Ward, 1981). This can induce different degrees of masculinization in the baby girl. Most probably, some masculinization of the girl's brain is an advantage. It is thought to add a certain degree of vigilance, toughness, and curiosity, which certainly ought to be an advantage for her when dealing with society as an adult woman.

What about the development of the female brain? In all likelihood it is regulated by a constant low level of estrogen during the whole prenatal and postnatal development. Girls with Turner's syndrome, lacking one X-chromosome (XO), thereby unable to produce estrogen, have a clearly different behavior from normal girls and from normal boys; their brains are more "neutral brains" (Murphy *et al.*, 1997; Ross *et al.*, 2000; Ranke and Saenger, 2001).

Male and Female Mental Profiles

The effect of testosterone in the fetus appears to depend on the levels of hormone, a dose/response effect. This has been demonstrated clearly in rats (Meisel and Ward, 1981), and is most certainly one of the reasons for the great variations we see around us in male characteristics and behavior among men and women. In fact, we are all distributed along a Gaussian curve, where there can be observed an overlapping population with genotype males (XY) and females (XX) who present male and female properties, bodily and, particularly, mentally. We all have met individuals who are very feminine men but father of many children, as well as masculine, aggressive women, who have given birth to children. But masculine women, like masculinized female rats, start menarche late, have some difficulties becoming pregnant, bear fewer children, and enter menopause earlier than females who were not influenced by male hormones during development.

It is important to consider statistics when discussing gender differences in the brain. A majority of individuals can be found around the mean/average, and the average may show large or small differences. However, there are always tails of the bell-shaped Gaussian curves that extend to the right and to the left, with fewer and fewer persons presenting extremes of the character in question.

We can, for instance, look at the statistical distribution of intelligence. This is a difficult property to identify, and is composed of many variables (spacial, verbal, mathematical); and men and women differ in these variables (Hedges and Nowell, 1994). As a way of expressing general intelligence the term IQ is used. The average IQ value is 100 by definition. Based on results in Hedges and Nowell (1994) and Kimura (1996), there is a larger number of women around 100 than men, but fewer women tail down toward IQ 60 than men, and fewer women reach IQ 150 than men. The thickness of the gray matter in the neocortex is on average greater in women than

in men, while the overall weight of women's brains is just below 1 kg. Men's brains weigh a little above 1 kg, a fact that has been taken as an indication that women, on the whole, are less intelligent than men. However, intelligence is more likely to be related to the ratio of gray matter/white matter (conducting nerve axons) rather than to total weight (Gorski, 2002).

Male/Female Brain Differences

The ratio of gray/white substance is greater in most women than in most men. Other differences can be seen in the corpus callosum, joining the right and left hemispheres. Parts of this structure are larger in women than in men (except in homosexual men), indicating a greater connection between the "logical" and the "emotional" halves of the brain (DeLaconste-Utamsing and Halloway, 1982; Allen *et al.*, 1991). It also suggests a greater simultaneous capacity in women compared to most men, and a better capacity to make decisions with long-term validity.

It allows the neocortex greater flexibility in the use of the brain. For example, most women have language representation in both hemispheres (Diamond, 1991), while most men only use one hemisphere for speech and language. Remember the Gaussian curves, however, because there are always many exceptions.

The greatest differences can be found in the old brain, in the hypothalamus (Gorski, 2002). Since this structure is responsible for reproduction, and since the human species uses sexual reproduction (not just dividing like bacteria), there is a male sexual behavior and a female behavior (LeVey, 1994). If we consider evolution, the capacities to eat, survive, and reproduce have been common denominators for existing species. Also we have the same centers to steer our reproductive behavior. These centers develop during the two developmental windows before and just after birth.

Two of the cell groups regulating this (INAH 3, and NSC) decide partner preference, meaning the people to whom we are attracted, man or woman, as a sexual partner (Allen *et al.*, 1989; Gorski, 2002). In homosexual men these two groups of nerve cells are as large as in most women, but there are variations (Swaab and Fliers, 1985; Swaab and Hofman, 1990; LeVey, 1991). These groups are fully developed around the age of 3-4 years, and become behaviorally evident at adolescence, when the final hormonal rebuild of brain connections occurs (a usually quite difficult period of life for parents as well as for the youth–many suicides occur in this phase of life). Thus, an individual cannot choose as an adult whom to be attracted to; moral and social codes have no influence. Only those in the overlapping population (there is always a Gaussian curve for everything) who may be bisexual can choose. Since these cell groups differ between men and women, and since they even differ in transmitter, their sending nerve terminals to the neocortex may well explain why men and women have different intelligence profiles, think differently, have different priorities, differences that should be used in society and respected from both sides.

Thus, homosexuality is not a disease and cannot be cured, and does not need to be cured. It is to be considered as a normal variation, found in all animal species. Homosexuality is present in about 8-10% of the male population over all racial or national borders (LeVey, 1994). It is a biological immutable built-in mental profile that should belong to each person's private life. An interesting fact is that some Indian tribes in North America have considered homosexual men as more valuable for the tribe than "normal" men, because the homosexuals represent a combination of male and female capacities (McGormick and Witelson, 1991), and are therefore looked upon as more complete, wiser, human beings.

The third group of nerve cells, BST, decides if we feel like men or like women. Transsexual persons have been studied, and this cell group seems to decide our gender identity (Zhou *et al.*, 1995). Thus, in these individuals the sex of the body does not agree with gender in the brain. These three, so far detected, cell groups can vary independently of each other, creating a rich pallet of conditions and minds. Most transsexuals are helped to a better and happier life after surgical and hormonal therapy to adjust their body in accordance with their mind (Landén, 1999). Other variables, for example transvestites, do not wish to alter their body, but need to express their femininity at times to feel content and happy in life. If we understand that this is biologically based, and cannot be altered by moral education, or punishment, we may be able to make better use of these individuals in society, since they are often highly intelligent and gifted.

Gender Resides in the Brain

Numerous studies have confirmed that gender is in the brain, not in the external genitals. Many maltreatment lawsuits have been started by boys who were raised as girls after surgical mistakes during operations to the external genitals. A famous example is the fraud Joan, described by J. Colapinto in "As nature made him; the boy who was raised as a girl." It is not possible to alter gender-typical behavior by upbringing or education.

The differences regarding gender-typical behavior between most women's brains and men's brains can be summarized as follows: The female brain uses more serotonin, is less influenced by testosterone, can work with both hemispheres (simultaneous capacity), has a great capacity for overview and long-term consequential planning/thinking. More women than men have greater social capacity, since the genes for this are located in the X-chromosome (Gillberg, 1999, pers. comm.), and women show, in general, greater empathy.

However, note that some men have female-type brains and some women have highly masculine brains. You do not automatically find a female type of talent in a XX person, but the statistical chance is larger than in XY individuals.

Are Men More Aggressive?

The basis for the gender differences in thinking and behavior is the number of offspring, just as in flora and fauna. Male plants and aminals produce far more pollen or sperm than the female counterpart produce ova. This explains male competition, male dominance, male aggressiveness, promiscuity, and risk taking (LeVey, 1994; Gorski, 2002). The mammalian male spends very little energy producing a large number of small sperm, so his strategy is spreading these around as much as possible. In contrast, the female has to spend a lot of energy in first producing the large ova, carrying the offspring during the long pregnancy, then nursing the newborn for up to two years. She then cares about the upbringing of the children, worries about their health, and helps the grandchildren. For a woman, sexual intercourse may mean a lifetime investment. For a man it is important to spread his sperm around, not needing to bother about the future, which explains promiscuity, and short-term thinking, well known in societies.

Males compete for women, jobs, positions, money, and power, just as other male mammals compete and fight for females, positions, influence, and power in the herd. A man must dominate over other males, and he uses aggression and fights for this. He must also be bold, and prepared to take risks, as a part of this male game-play. The bold, aggressive, dominant male can spread his genes better than other men. In civilized societies we do not expect to see this behavior openly, but it does indeed exist.

Balance Between Serotonin and Testosterone

It seems that the mood and behavior in humans is due to a balance between serotonin (and some peptides) and testosterone. Fighting between young rhesus monkey males is directly related to levels of the hormone. Females do much less fighting and have low testosterone levels. In humans, there is also a well demonstrated relationship between violence and crime, and testosterone levels, which is also directly related to age. War is often started due to the influence of testosterone, involving mainly young men with high hormone levels who are involved in and often enjoying aggression. But testosterone is also a positive hormone, responsible for initiative, curiosity, vigilance, and endurance when balanced by other active neurochemicals and education of the neocortex.

Increased serotonin transmission induces harmony, positive feelings, a sense of enjoying life, and promotes good social interactions. An increase in testosterone induces aggression, fights, competition, feelings of revenge, arrogance, but also heightened vigilance, curiosity, determination and strength, so important for the progress of mankind. The frontal lobes, involved in long-term planning activities and

strategies, are densely innervated by serotonin nerve terminals, and by dopamine terminals, which are involved in the reward pathways. These areas are also rich in 5-HT1a receptors, more numerous in women than in men. If we can balance testosterone action (for instance by developing suitable testosterone receptor-blocking agents), and increase serotonin levels, we may reach a situation where logical reasoning can replace fighting, aggression, and war.

Women's Health Problems Caused by Males

The health of women is largely influenced by male society, and by individual men in their families. The prevailing attitude against women is sadly disrespectful and arrogant in many parts of the world, not the least in western societies. To tolerate this from a man with a lower IQ and with poor education can be depressing for an intelligent woman. This arrogant behavior of "I know best because I am a man" is related not only to society and culture but also to testosterone levels.

In fact, most of the health problems for women in the world are caused by high testosterone in males. Rape, violence, abuse, spread of HIV/AIDS, cancer of the uteral cervix, and too many child births resulting in malnutrition and mental exhaustion, are all caused by the uncontrolled effects of testosterone. Unfortunately, male politicians and male religious representatives have little interest in these problems. The introduction of birth control methods, like the easy and cheap condom, is often hindered, and correct information about contraception is actively suppressed. The use of condoms, which also prevents the spread of HIV, is not encouraged since the factual existence and spread of HIV is denied by some leaders.

Empower Women

Complementary to efforts at high political levels and industrial bioscience enterprises to promote health and decrease poverty in the developing world, we also need to support activities at the grassroots level. Women are more clever in using mini-loans as demonstrated by the World Bank, and the example from India. The fact that women in developing countries now do 80% of agricultural labor, but only receive 10% of the income, should clearly indicate that aid to developing countries should be directed/earmarked to women.

It is known that most women are by nature and/or need, caretakers of children and of the family, and their social competence and sense of responsibility may be life-saving for many groups of families. It is also a general observation that some men in developing countries tend to escape the harsh reality by turning to alcohol, drugs, and promiscuity, a typical flight/avoidance behavior.

Leaders, at all levels, must realize and acknowledge that there are indeed differences between most men and most women, and that attitudes, intelligence profiles, and strategies in the two sexes are different, but complementary. Only by recognizing and respecting the differences on an equal level, and acknowledging the importance of the life-supporting activities, in family, in schools, and in hospitals, can the intelligence of people flourish.

How do we disseminate acceptance of the mental differences in thinking and planning, and respect for women's intelligence? For the prosperous development of society, it is most important to counterbalance the sometimes arrogant and patronizing attitude of many men toward female work and inventiveness.

When women are empowered and educated, they in turn can influence and educate their children. The first 4-5 years of life are important to imprint inner security and a positive constructive picture of the outside world in the growing neocortex. School will then play a major role, with liberal education, allowing positive thinking, criticism, and open discussions, and combating negative attitudes between genders. Universities that teach natural sciences to humanity and religious students are imperative.

It is important for the developing brain to meet other "brains" with different and special experiences. People of all ages, genders, cultures, and religions should meet freely and recognize the wonderful spread of qualities, ideas, personalities, and minds that exist. Meeting others without bias and prejudice helps people realize that we share similar values in life. Youngsters from different cultures should travel to new places and attend cultural events and scientific seminars. An historic and geographic place most suitable for these meetings is Bibliotheca Alexandrina, and funding for this is encouraged.

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References

Allen, L.S., M. Hines, J.E. Shryne, and R.A. Gorski. 1989. Two sexually dimorphic cell groups in the human brain. J. Neurosci. 9, 497-506.

Allen, L.S., M.F. Richey, Y.M. Chai, and R.A. Gorski. 1991. Sex differences in the corpus callosum of the living human being. J. Neurosci. 11, 933-942.

Åsberg M., P.Thorén, and L. Träskman. 1976a. "Serotonin depression"–A biochemical subgroup within affective disorders? Science 191:478-480.

Åsberg M., L. Träskman, and P. Thorén. 1976b: 5-HIAA in the cerebrospinal fluid: A biochemical suicide predictor? Arch. Gen. Psychiatry 33: 1193–1197.

DeLaconste-Utamsing, C., and R.L. Halloway. 1982. Sexual dimorphism in the human corpus callosum. Science 216, 1431-1432.

Diamond, M.C. 1991. Hormonal effects on the development of cerebral lateralization. Psychoneuroendocrinology 16,121-129.

Gorski, R.A. 2002. Sexual differentiation of the nervous system. In: Principles of Neural Science, 4th Edition, Eds: E.R. Kandel, J. H. Schwartz, and T. M. Jessel. Chapter 57, pp. 1131-1148.

Hedges, L.V., and A. Nowell. 1994. Sex differences in mental test scores, variability, and numbers of high-scoring individuals. Science 269, 41-45.

Kimura, D. 1996. Sex, sexual orientation and sex hormones influence human cognitive function. Curr. Opin. Neurobiol. 6, 259-263.

Landén, M. 1999. Transsexualism. Epidemiology, phenomenology, aetiology, regret after surgery, and public attitudes. MD Thesis, Göteborg University, Sweden Parajett AB, ISBN 91-628-3877-6.

LeVey, S. 1991. A difference in hypothalamic structure between heterosexual and homosexual men. Science 253, 1034-1037.

LeVey, S. 1994. "The sexual brain." The MIT Press MIT, Cambridge, Mass.

McGormick C.M. and S.F. Witelson. 1991. A cognitive profile of homosexual men compared to heterosexual men and women. Psychoneuroendocrinology 16, 459-473.

Meisel, R.L., and I.L. Ward. 1981. Fetal female rats are masculinized by male littermates located caudally in the uterus. Science 213, 239-242.

Murphy, D.G., M.J. Mentis, P. Pietrini, C. Grady, *et al.*, 1997. A PET study of Turner's syndrome; Effects of sex steroids and the X-chromosone on brain. Biol. Psychiatry, 41, 285-298.

Nishizawa, S., C. Benkelfat, S.N. Young, M. Leyton, S. Mzengeza, C. de Montigny, P. Blier, and M. Diksic. 1997. Differences between males and females in rates of serotonin synthesis in human brain. Proc. Natl. Acad. Sci. USA 94, 5308-5313.

Ranke, M.B., and P. Saenger. 2001. Turner's syndrome. Lancet 358, 309-314.

Ross, J., A. Zinn, and X. McCauley. 2000. Neurodevelopmental and psychosocial aspects of Turner's syndrome. Ment. Ret. Dev. Disabil. Res. 6, 135-141.

Swaab, D.R., and E. Fliers. 1985. A sexually dimorphic nucleus in the human brain. Science 228, 1112-1115.

Swaab, D.R., and M.A. Hofman. 1990. An enlarged suprachiasmatic nucleus in homosexual men. Brain Res. 537, 141-148.

Toran, Allerand C.D. 1984. On the genesis of sexual differentiation of the nervous system, morphogenetic consequences of steroidal exposure and possible role of a-fetoprotein. Progr. Brain Res. 61, 63-98.

Van Praag, H.M., and S. de Haan. 1980. Central serotonin deficiency–A factor which increases depression vulnerability? Acta Psychiatrica Scand. (Suppl 280):89-95.

Zhou, J., M.A. Hofman, L.J.G. Gooren, and D.R. Swaab. 1995. A sex difference in the human brain and its relation to transsexuality. Nature, 378, 68-70.

Chapter 27

Global Partnership of Scientists, Doctors, and Patient Organizations

Ysbrand Poortman

Introduction

About 80% of the world's population lives in low-income countries. In addition to poverty, developing nations are characterized by economic dependency, lesser urbanization, poor technological development, and deficiency in well-trained people.

This translates into low education levels, high fertility, high maternal mortality, ineffective family planning, barriers to access to safe abortion, reduced life expectancy, preventable morbidity and mortality, underfunding of health services, distorted health priorities, and inequitable access to services. About 90% of the world's children are born in developing countries, with an estimated 3.3 million born with birth defects yearly.

Many diseases have a genetic origin or component. This includes many forms of cancer, cardiovascular disease, diabetes, rheumatism, neurological and psychiatric diseases, and many rare disorders. Various infectious diseases have a relationship with a genetically determined immune system.

Genetic diseases and birth defects are conditions that are generally speaking without cure, without effective treatment, disabling, lifelong, and have high physical, psychosocial, and economic implications for individuals and families.

Depending on the condition, 10-30 % of genetic diseases and birth defects can be prevented if the present expertise and care provisions reached the people in timely fashion.

Partnership of Scientists, Clinicians, and Patient Organizations

In April 1994, people from 25 countries met in New York at the invitation of the March of Dimes Birth Defects Foundation. They addressed the worldwide issues of genetic disease and birth defects. This meeting led to the start of the World Alliance of Organizations for Prevention of Birth Defects (WAOPBD). In 2003 the name was

changed to World Alliance of Organizations for Prevention and Treatment of Genetic and Congenital Conditions (WAO, 2000; WHO, 1999, 2000).

The participants declared: *"We are dedicated to the prevention, cure and amelioration of genetic and congenital conditions and we want to decrease the gap between new scientific discoveries and their practical application in health care and prevention."*

The alliance is incorporated under Dutch law and its secretariat is located in Soestdijk, The Netherlands. What makes the alliance unique is the focus on collaboration of all parties involved, and especially with groups in low-income countries and with patient organizations. The constitution allows two seats for representatives of patient organizations and half of the members of the board come from developing countries.

The alliance chose to focus on preconception and perinatal care in developing countries as one of the most urgent fields of attention, and to achieve its goals by sustainable partnerships among international organizations committed to the prevention of chronic/genetic disease and birth defects, and adequate care of affected individuals and their families.

Statement of Principles

The members adopted a statement of principles to make clear their common views on ethical affairs and priorities:

- Respect for persons with disabilities.
- Protection from stigmatization and discrimination.
- Primary prevention, as the most important goal.
- Incorporation of prevention as a routine component of health care systems.
- Dedication of a proportion of every health budget to the prevention of genetic disease and birth defects.
- Dissemination of knowledge about prevention to prospective parents.
- Commitment of all countries through public policy to the prevention of birth defects.
- Collaboration of experts and multidisciplinary approaches.
- Involvement of lay interested parties, families, and volunteers.
- International communication and sharing of information.
- Universal access to preventive, therapeutic, and psychosocial services.
- Involvement of a wide range of professionals.

Achievements of the Alliance

To achieve its goals, the alliance organizes regional conferences, always in partnership with regional groups and focusing on needs determined by these groups. By 2004 there were 14 major conferences in 13 countries leading to better integration of services, more public awareness, and recognition by authorities.

Some of the conferences resulted in declarations that reflect the needs of the region. The Cape Town declaration (South Africa, November 1997): *"In order to meet the needs of the developing world with respect to birth defects, we recommend that partnership between developing and industrialized countries be encouraged; the important role and involvement of support groups be recognized and information be disseminated to the public at large, groups at risk and to health care professionals. In planning the implementation of these recommendations, resources need to be mobilized in order to generate the capacity of the developing countries to play an active role in this process."*

The Amritsar (India, 4 December 1998) declaration: "As a consequence of their role in society in many developing countries the impact of the birth of a child with a birth defect falls particularly heavy on women. The lack of appropriate services and support makes them especially vulnerable and endangers their reproductive health. There is an urgent need for resources to be invested that will give access to information, services and support to empower women, free them from stigmatization and discrimination and enable them to make free choices on reproductive options and help them to live healthily. A well resourced network of genetic centers will facilitate these goals."

A number of activities took place in collaboration with the World Health Organization. One of them was a WHO/World Alliance expert meeting in The Hague in 1999, where 27 experts from 19 countries participated. They identified the following needs:

- Chart and recognize the burden imposed by genetic disorders and birth defects.
- Improve epidemiological knowledge about genetic disorders and birth defects.
- Define goals of genetic services in terms of individual family well-being and public health.
- Improve prenatal and perinatal services.
- Organize genetic services in a comprehensive and integral manner with roots at the primary health care level.
- Educate the public about genetics.
- Encourage political will and commitment.
- Encourage the formation of parent/patient organizations.

The alliance decided recently to give priority to the formation of patient organizations. This has resulted in the formation of various national and regional alliances (India, Ukraine, and South America), and the creation of an International Genetic Alliances (IGA) of parent and patient organizations.

Strategic Issues

At least 90% of the national budgets for health care goes to the management of disease and about 1% to prevention of disease. The options for prevention of disease have increased enormously. Screening and early detection of disease, genetic services and family planning, immunization of newborns, and many other facilities could greatly contribute to improved health.

These services are often cost effective, whereas the societal costs of inaction, measured in terms of avoidable human suffering and burden to public health, are very high.

The alliance strives to influence policy and decision-makers on the basis of the individual, family, and community burden of disease, reliable epidemiological data, available expertise in the region, potential expertise (training and education), and options or models for best medical practice.

The International Clearinghouse Birth Defects for Monitoring Systems (ICBDMS) is an example of how the alliance can offer expertise, through this collection of data, and the exchange of information. The reports and the World Atlas of Birth Defects are of great value.

The contribution of the parent and patient organizations are also of particular importance, through their knowledge of the bottlenecks and gaps in health care, and the impact of disease, and their capacity to have an input into the political arena and to influence society via the media.

International Genetic Alliance

The alliance was founded in Lyon at the occasion of the Third Global Life Sciences Forum in 2003. The scientific environment proved to be an ideal location for communication and collaboration. This alliance works with the associations that focus on disability and handicap.

The alliance chose as a vision *to seek a world where genetic conditions are understood, prevented, treated, ameliorated, and cured.*

Its mission reads: *to promote medical genetic services, research, technologies, and access to information, in order to alleviate the burden of genetic conditions for individuals, families, and communities.*

The following guiding principles were formulated:

- All individuals, regardless of their genetic condition, culture, race, ethnicity, beliefs and/or socioeconomic status, deserve equal rights and opportunities, without prejudice, discrimination or stigma.
- Relevant social, ethical and legal protections are critical to the progress and translation of basic science to services.
- Worldwide information sharing and resource exchange, with respect to diversity,

increases capacity and decreases disparities.

- Meaningful global progress in policy, health care and research requires a patient/parent network in partnership with health professionals, industry and policymakers.
- Applications of education, medical genetic services, research, and biotechnology alleviate the burden of genetic conditions.

The objectives:

- Support and accelerate research to prevent, treat, ameliorate and cure genetic conditions, through the translation of biotechnologies to accessible services.
- Develop policy in partnership with policymakers.
- Engage in partnerships with clinicians, researchers, industry, and nongovernmental organizations with a shared mission.
- Establish best practice in medical genetic services that respects the autonomy of the individual, family, and community within a cultural context.
- Ensure access to relevant information, services, technologies, and medical treatment.

Role of Patient Organizations

These organizations strive to make government officials and political leaders aware of new genetic knowledge and its applications.

Parents' and patients' organizations tend to work closely with academic clinical genetic centers. With their support, they are able to produce comprehensive educational materials for the general public, which includes audiovisual presentations, audiotapes, and lesson packets for schools. They also produce television programs in the context of Open University programs; they establish public awareness campaigns that spread information about the availability of genetic services.

Recent campaigns address the importance of folic acid as a primary preventive in the preconception period.

These organizations also take stands on topics such as patenting of genetic material, the various international declarations pertaining to the human genome in the context of human rights, and the need for genetic services throughout the world.

The media and the political leaders have shown an increasing interest in the opinions of parents and adult patients who have become experts themselves because of their personal experiences. Another potential is their contribution to research efforts by encouraging their members to participate in biomedical research, recruitment for trials, and participation in trial protocols.

Patient organizations evolved gradually from a state of helplessness in the 1970s, via a state of emancipation toward management driving the future of health care. They are setting up global networks and regional collaboration with scientific groups that have an interest in their disease-specific needs. They also develop in low- and medium-income countries, and in India and Ukraine where there are well organized patient alliances. They work in close communication with academia and health care systems on the national and regional level. All are united in the International Genetic Alliance, which works in partnership with the World Alliance and in structural collaboration with the Global Life Sciences Forum and the International Federation of Human Genetic Societies.

Conclusion

The fast expanding networks of patient organizations, and the increasing collaboration between them and the scientific and clinical community, has a positive influence on the quality and efficiency of health care.

The World Alliance of Organizations for Prevention and Treatment of Genetic and Congenital Conditions as a global partnership of scientists, doctors, and patient organizations is an effective instrument to contribute to the prevention and management of genetic and congenital conditions.

References

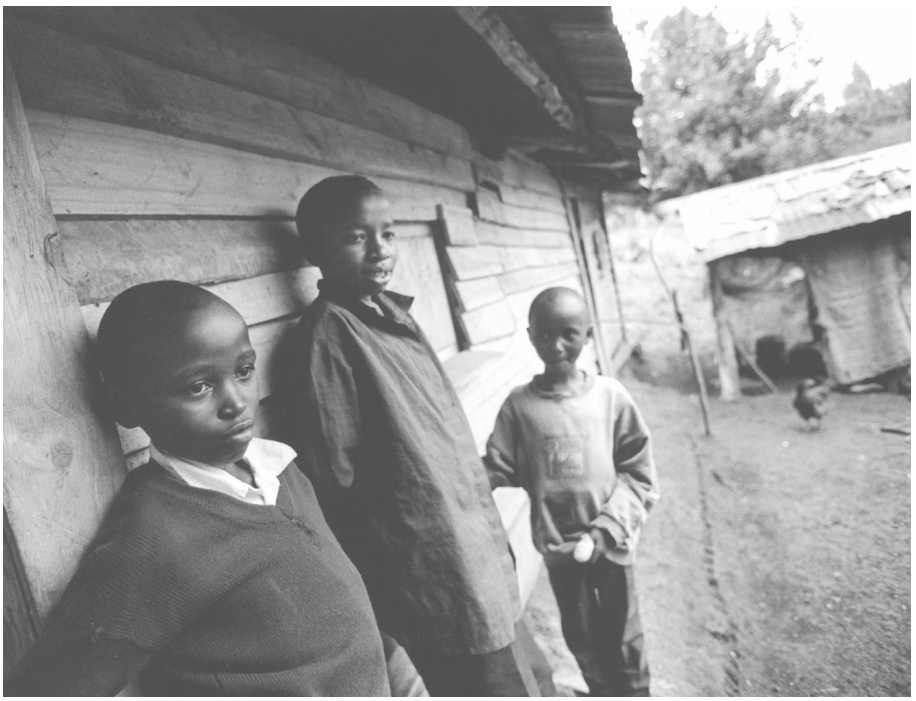
World Alliance of Organizations for the Prevention of Birth Defects. 2000. Society and genetics. WAOPBD, VSOP, Soestdijk, The Netherlands.

World Health Organization. 1999. Services for the prevention and management of genetic disorders in developing countries. WHO/WAOPBD, WHO, Geneva, Switzerland.

World Health Organization. 2000. Primary health care approaches for prevention and control of congenital and genetic disorders. WHO, Geneva, WHO/HGN/WG/00.1.

Section 6

Ethics, Patents and the Poor



Chapter 28

Institutional Landscape, Legal Issues and Policy Setting, and Funding Research

Alexander von der Osten

Introduction

The importance of institutions in science appears obvious, yet it is not always recognized. Institutions represent the setting in which science works. They reflect the culture in which scientists interact, collaborate and reach out. They represent the means for organizing research and for producing results. Experience shows that institutions do make a difference. They have a bearing on the creativity of scientists and on the productivity of research investments. A dynamic institutional setting will prompt innovation, inspire scientists, promote interaction, stimulate partnerships, and enhance productivity. Furthermore, it will attract young scientists, promote excellence, and facilitate the interaction between science and society at large.

Institutional Landscape

Changes in the institutional landscape have accelerated in recent times. A number of developments and trends merit brief mention.

Knowledge is more important today for future economic success than the possession of material goods and resources. Much of what is changing today is driven by science and technology (S&T). Increasingly S&T is the engine of development. Hence aggressive investment in the buildup of their knowledge systems and the expansion of their S&T capacity is ever more crucial for developing countries.

When seen from the outside, progress in science appears to occur in jumps or breakthroughs; on the inside there is increasing recognition of the critical importance of scientific capital (the accumulated stock of scientific knowledge) for technological progress. Science is a cumulative endeavor with a kind of snowball effect. One round of innovation sets in motion additional efforts that will lead to further innovations.

The stock of knowledge–or scientific capital–largely determines the present and future productivity of research investments, and hence the speed and magnitude of future innovation and economic growth. The real magic of science stems from the patient and persistent accretion of new knowledge. It is the accumulation of research results over the long term that accounts for the differences in agricultural productivity around the world. This in turn underlines the importance of strong institutions, sustained effort, and continued support. Stability and continuity are key conditions for success. Irregular funding is not helpful, and severely limits progress. Disruptions in the flow of funding and in research activities are harmful and can have catastrophic consequences.

Money is important; funding for research and development (R&D) is essential; but creating an appropriate science culture may be even more important. This culture, along with appropriate policies and practices, will foster the accumulation of knowledge, innovations, and technologies, and thus help to build up the scientific capital base. It will stimulate investments in R&D activities and the continued buildup of scientific capacities–through training of first-class scientists and the strengthening of institutions of excellence. This is probably the key difference between successful developing countries and those that lag behind.

Privatization of science and technology

Private R&D has expanded dramatically since the 1980s, particularly in the industrial countries. Overall, private research today accounts for well over 50% of all research in the North (in real numbers: roughly US$11 billion of a total research budget of US$21 billion), and for around 5.5% in the South (in real numbers: US$0.7 billion out of a research budget of US$12 billion). Growth in private sector investments continues in the North and South, albeit at considerably more moderate rates in the developing countries. Growth rates in the North are impressive, particularly in countries like the USA, where commercial crop breeding for commodities with great market potential is dominating the scene.

The area planted to bioengineered crop varieties in 2002 was estimated at 58.7 million hectares. More impressive than the actual area is the rate of expansion–well over 10% per year. In 2002 four countries accounted for 99% of the global total, the USA leading the way with two-thirds of the total. The developing world share of the global area presently stands at approximately 27%. For the time being the dominance of the North is still continuing, in terms of conducting the research and utilizing the products. Private firms do much of that work.

Both trends are facts of modern life. Through mergers and acquisitions a few chemical and seed companies in the North are expanding their market shares and spheres of influence. The result: a small number of global players, mostly multinational firms, increasingly dominates the market. In Asia 50% of private R&D is already in the hands of multinational corporations.

Technology gap between South and North

Research investments in the developing countries average 0.6% of agricultural GDP compared with 2.6% (public research spending) in the industrial countries. To prevent this gap from widening, developing countries need to invest aggressively in S&T. Reliance on technology import only is not a wise policy option. Local capacity needs to be built up wherever this is meaningful, in collaboration with others, such as neighboring countries or countries with similar agroecological circumstances.

There is growing underinvestment in public sector research and development in developing countries. The principal causes of this development: structural adjustment, austerity, a general retrenchment in the public sector, fiscal crises, policy reform, a certain complacency in the light of improving food balances and growing private sector investment, and the erroneous belief that "the private sector will take over those functions." The effects of this: a decline of public sector national agricultural research institutes (NARIs) in the South. These institutions have been losing part of their support and suffering an erosion of their scientific capacities. Scientists have left for better opportunities elsewhere; attracting and retaining the young and well trained is increasingly difficult.

There is a growing awareness of the needs and benefits of collaboration. Working in isolation is not a wise option, certainly for developing country NARIs. The challenge ahead is to develop innovative forms of collaboration and partnership that maximize returns to all partners involved. This includes public-private partnerships.

The future institutional landscape in developing countries prompts some central questions: how fast will private research expand; will this expansion of the private sector effectively compensate for the decline in public investments; will private research eventually replace the public sector? The answers are clearly no, not any time soon. The reason is that the private sector depends on cost recovery and profit. As profitable markets develop in the longer term and conditions for cost recovery improve, the private sector will undoubtedly play an increasingly important role, but this will take time. And not all research functions lend themselves to private sector execution.

The private sector targets its investments at those products, producer groups, and ecologies that are attractive in terms of promising appropriate returns to investment. The main criteria for targeting private investments therefore are: market size and the appropriability of returns–that is the capacity for the investor/inventor to capture part of the gains from research.

Large sectors and client groups in developing countries are not attractive in terms of these criteria. They will not be served by private research and hence will remain dependent on the public domain for a long time to come. They comprise the following categories:

- Products/commodities with weak markets, in particular orphan crops.

- Client groups with limited purchasing power, such as smallholders and poor farmers; this includes the totality of subsistence agriculture.
- Ecologies where returns are limited, in particular low potential areas.
- Tasks that do not yield returns via the market, such as the conservation of genetic resources and natural resource management research.
- Basic research and much of pre-technology research; the training of scientists.
- Components of biotechnology research for which it is hard to appropriate the benefits privately.
- Work related to biosafety regulations and regulatory processes.

In most developing countries most of the research functions are thus bound to stay in the public domain, at least in the near to medium term. The principal reasons:

- Public good nature of much of the research.
- Market failure.
- Economies of scale and externalities.
- Long-term and risky nature of research.
- Regulatory setting and IPR legislation which, while improving, are still not very favorable to private R&D.
- Business environment: in most places a business climate prevails which, while getting better, is still not sufficiently attractive to private investment.

Complementarity of public and private research

On balance then, the private sector is no substitute for public research. Both are needed; both contribute to the well being of society; both have important contributions to offer; and both are essential components of a functioning research system. They are different, in functions, motivations, approaches, priorities, and strengths and weaknesses; but they complement each other.

Frequently, skepticism and concerns are voiced regarding the value to society of private research. These concerns are largely unfounded. There is considerable empirical evidence that private research (where it occurs) does contribute to the well being of its clients. Farmers are well served on the whole.

Looking ahead then, we note that in developing countries the public sector will retain a critical role. Public institutions will need to carry the bulk of R&D work for a considerable time to come.

In this connection we need to remember that public sector research functions are distributed in different ways in the South and North. Although in the North about 43% of public research is done by universities, that share is considerably lower in the developing countries. Where the bulk of public research is carried out by NARIs, that is governmental or parastatal organizations.

However, many of the old and once highly successful public sector NARIs are no longer fit to carry that burden effectively. They ran out of steam; they are showing

signs of ageing; they lost their vitality, their support by stakeholders, and part of their funding. They need to reform. They need to reinvent themselves as modern enterprises in S&T that function as true centers of innovation and serve their clients effectively.

The NARI reform agenda can be summarized in seven key action points:

- *Reposition*. Define the mandate in relation to other actors, in particular the private sector. Avoid duplication and competition with the private sector. Foster complementarities and collaboration. Refocus the program on public goods, emphasizing the benefits to society. Leave to the private sector what they can do - and will do.
- *Reorganize* and revitalize. Downsize, or better right-size, focusing on the essential; restructure; streamline the organization, always remembering that form follows function. Show vision, and replace the old dominance of bureaucracy with a new business culture.
- *Strengthen the quality of science*. Secure access to the most recent tools of science, which are often in the hands of universities or private sector organizations. Connect with the private sector, both national and international–North and South. Key: build stronger bridges with the universities.
- Create a truly pluralistic research system. Such a system is outward looking–ready to partner with institutions of advanced science and downstream activities in the public and the private sectors. This implies an important change in organizational culture.
- *Reinforce the client orientation.* Stakeholder participation in governance and priority setting is key. This requires transparency. It builds ownership, regains confidence, strengthens accountability, and builds support (political and financial).
- *Reach out*. Strengthen the information function and build capacity for effective communication. Informing the public builds trust. Seek presence and active involvement in the public policy debate on S&T policy. After all, the voice of NARS has legitimacy and credibility; it needs to be heard.
- *Pay attention to legal and regulatory aspects* of the business. This is the other side of the coin; it is no less important for success and impact. It is crucial therefore to upgrade skills in intellectual property rights and business management.

The task is to build a dynamic research and innovation system that is able to face the challenges ahead. Such a system will attract others to join and collaborate, including new partners, alternative funders, and providers of research, thereby expanding the resource base.

Forging alliances, building partnerships

Today more than ever, partnerships are an essential feature of any functioning research system; after all, the world of science lends itself especially to collaboration. Working in isolation is not a viable option. The number of research partnerships is increasing exponentially; it has become a common feature in South and North. Successful NARIs are increasingly engaging in partnerships. An interesting example in this connection is EMPRAPA, the Brazilian research corporation and one of the most successful research ventures. EMBRAPA is managing hundreds of partnerships with a broad range of institutions in the South and North.

Partnerships comprise many constellations, involving different types of partners: public/private, South/North, national/international. They comprise different modalities of collaboration, ranging all the way from contract research and cofinancing arrangements via loose associations (often project based) to joint ventures and other institutional instruments.

Public/private partnerships appear to be an approach with great promise. In terms of numbers, public/private partnerships are probably still well below their potential. After all, the complementarity of both sectors offers attractive opportunities for collaboration in both research funding and the execution of research functions. Given the different strengths of both, there is ample scope for efficiency gains through collaboration, for win-win strategies. There are prospects for public funding of private research to tackle technology problems concerning developing countries.

There is ample scope for innovative forms of partnerships. Opportunities for win-win strategies are waiting to be harnessed. The goals of public and private institutions are different, but they can be compatible. There are opportunities for public sector NARIs to serve societal goals while respecting and protecting the legitimate interests of innovators and private investors. Also, the potential role of private not-for-profit organizations will need to be explored in this connection. Given their special characteristics, they may well play a catalytic or bridging role between public and private organizations.

Two well known success stories of public/private collaboration in plant breeding that are generating important benefits for poor farmers and consumers are *"golden rice"* and *"quality protein maize"* (QPM). Both represent cereals that have been modified in ways that offer broad social benefits. Both incorporate characteristics that deal with human nutrition problems. The key to success is the joining of forces between public and private institutions, each contributing specific components to the complex research agenda. Private companies have little incentive to invest in products that large commercial farmers are not normally willing to pay for. Here the public sector comes in.

Legal and Policy Setting

In agriculture, intellectual property protection is a fairly recent phenomenon. For centuries new crop varieties–or technological progress in general–were treated as common property, shared freely among farmers and countries, and generating huge profits for all concerned. Beginning in the 1980s a revolution occurred in the effective protection of property claims particularly relating to agricultural biotechnology. Since then the era of free access to new varieties appears to be passing into history. By now, several protection regimes are in place: TRIPs (World Trade Organization), the Patent Cooperation Treaty (World Intellectual Property Organization), and the International Union for the Protection of New Varieties of Plants, among others.

Another complication arises from the fact that just like the research products themselves (mostly improved crop varieties), the scientific tools and processes used to produce those products are increasingly encumbered by intellectual property protection.

It is well accepted by now that the protection of intellectual property is a mixed blessing. On the one hand it provides incentives to innovate, to invest, and to reveal new knowledge that might otherwise be kept secret. On the other hand, the cumulative nature of agricultural research implies that the proliferation of patents makes the handling of that aspect increasingly complex, costly, and time consuming. Also, of course, like all exclusion mechanisms, it bars important sectors of society from access.

Considerable controversy arises from the fact that there is heavy concentration of protected knowledge and technology in the hands of a small number of large multinational corporations based in the North. Access for developing country institutions (both public and private) is thus becoming increasingly difficult. There are efforts to address the problem of access to both processes and products of technology, but these have yet to be fully developed in ways that allow poor people in developing countries to benefit from progress.

Interactions on biotechnology between government, industry (life sciences on the one hand and agriculture on the other), and society have been weak on the whole–particularly in Europe, less so in the rest of the industrial world and in developing countries. Science has been largely absent from the public debate on regulatory matters and on the acceptance of biotechnology (processes and products). The effects of this of this defective interface have basically been negative for all concerned: no real winners and many losers.

The continuing controversy concerning GM foods is particularly strong in Europe, where large segments of the public continue to reject the production of bioengineered foods. This rejection targets products and processes. The basis of this rejection: lack of confidence by the public in the processes and products of the modern life sciences.

The regulatory systems in place fail to do justice to society (in terms of dealing with safety and ethical concerns) and industry (in terms of efficiency concerns and cost considerations). The task ahead: design new regulations that are viable, effective, and able to convince the public.

An increasing weight of regulatory processes creates an unnecessarily heavy burden on industry (in terms of time and cost). This is causing a slow-down in the testing and release of new products from biotechnology research; a delay in the approval processes; and thus a disincentive for investors who fear the enormous legal costs and delays involved in the development of new biotechnology-derived products.

Relevant questions are: how have other industries managed that interface? We know that life sciences in the health sector have been more successful in dealing with those matters. Does the health sector have any lessons to share with the agriculture and food industry? How best does one proceed to build public support for technological progress in agriculture?

Funding of Research: Investment Levels–Recent Trends

The simple truth is: pay-off to research investments has been high all along, it still is high, and is set to remain high for the foreseeable future. The yields of most major crops in the developing countries grew rapidly thanks to the joint efforts of national and international research organizations. Average grain yield doubled since the 1960s–an important contribution to food security, economic growth, and poverty reduction (through the decline in real food prices). According to a major review of hundreds of studies on rates of return, the median rate of return on investment is 43% for agricultural research performed in developing countries, and 46% for industrial countries.

Commitment to technological progress

As the importance of S&T for technological, economic, and social progress is gaining recognition, the need for investing in S&T, too, is increasingly considered important. It is a well accepted fact today that high levels of investment in R&D tend to lead to strong economic growth and social progress. Research intensity–the amount of research spending in relation to agricultural output–is an important indicator of this commitment.

Industrial countries as a group have been investing around 2.6% agricultural GDP in public sector R&D, in addition to substantial investments in private research. Developing nations as a group, in turn, have been investing around 0.6% of agricultural GDP in public research, with little private research spending in addition

to that. While there are enormous differences between developing countries, taken as a group, they lag far behind the industrialized world in terms of research intensity; and the gap is widening. Phillip Pardey and coworkers have calculated that in 1995 total research spending intensities (comprising public and private) were eight times higher in rich nations than in poor countries. As a result, the technology gap is likely to widen further.

We noted with great concern the North-South divide in research spending. But within the group of developing countries too, there are enormous differences in research investments between regions and countries. Three counties–China, India and Brazil–account for roughly 44% of total public research spending in developing countries. With regard to regional patterns, Asia is the most dynamic region, and Africa is the least, with investments being particularly low.

An increasingly important method of research funding in North and South is funding by technology users, that is the farmers–via commodity levies or commodity taxes. The main benefits of this are direct involvement of farmers in overall governance and decision-making (particularly agenda setting), a sense of ownership, accountability, stability, and continuity of funding flows. Australia offers an interesting example of successful user involvement. There is a long history of joint funding by producers and government. Producers have been contributing some 42% of the total, government matching grants the rest. Important for the success of this model is the existence of strong producer organizations. Overall, Australia thus represents a high level of private research funding (one of the highest in international comparison), a high research intensity, and good marks on stability.

By the mid 1990s about one-third of the US$33 billion total investment in agricultural research worldwide was private. In absolute numbers this amounted to US$11.5 billion. Yet, little of that occurred in developing countries–just US$0.7 billion or 5% of the total private investment globally (of a volume of US$11.5 billion). The overwhelming majority of private investment around the world–US$10.8 billion or 94.5% of the global total–is conducted in the industrial countries. As we pointed out, in developing countries private investment is still modest for a number of reasons. Taken as a group, developing countries presently account for some 5.5% of the global total.

As mentioned before, public research funding continues to be the major source of support in developing countries. In the North too, public sector research continues to maintain an important share in total R&D investments–with 48.5% of total research spending at present. In the developing countries research investments in the public domain have grown somewhat after years of decline–but very unevenly distributed. As a group, developing countries now account for some 53% of total public research of 21.7 billion international dollars adjusted for purchasing power differences between countries.

While we know that the bulk of biotechnology investments occur in the industrial countries, exact spending figures are hard to come by. There are enormous differences between countries; the USA and Canada are clearly leading the way (with

some two-thirds of the global total). Eighteen other countries are dividing the remaining third among them. Among the developing nations, Argentina and China (with some 4% of the global total) seem to be ahead of the rest. The remaining developing countries share some 12% of the global total.

The lag between investments in innovation and reaping the rewards is still substantial. Any major reduction of that lag is not in sight at present. The key factors responsible for the length of the lag are the research process itself (the actual development of new products), testing in different environments (time requirements tend to increase due to more complex regulatory procedures), and legal approval processes (time requirements are tending to grow).

After many years of strong support for agriculture and agricultural research, international development assistance agencies and many bilateral donors have cut back their support for both. Attention has shifted away from agriculture to such areas as economic infrastructure, health, education, and other social services.

Conclusion

Support for technological progress in developing countries must be mobilized. This will obviously include a range of measures:

- Transforming the policy dialogue: raising the visibility of the food and agriculture sector and the S&T community. S&T needs to be involved in that dialogue; it needs a place at the table.
- Reform of public sector NARIs–converting these institutions into more effective instruments and thus making them more attractive to investors. This will spur increased government funding and recognition as viable partners.
- Reform the legal and regulatory environment: create incentives to attract private sector investments in R&D. As intellectual property regimes become stronger, the business climate improves, and international trade in (agricultural) science and technologies grows, private investment will no doubt come in more strongly.
- Strengthening the effectiveness of resource use–making sure that investments are optimally used and produce the desired results.
- Raise the voice of developing countries in international forums, and contribute to informing and educating northern audiences that have a bearing on development assistance flows and the creation of conditions of fair trade.

Chapter 29

Creating, Protecting, and Using Crop Biotechnologies Worldwide in an Era of Intellectual Property

Philip G. Pardey, Bonwoo Koo, and Carol Nottenburg

Introduction

Most crops are grown in places where they did not occur naturally–they were introduced, either incidentally or intentionally. In this way, the development and dissemination internationally of new and improved seed varieties has been the basis for productivity improvement in agriculture since crops were first domesticated about 10 millennia ago. Initially the movement of plant material involved farmers carrying seed as they migrated to new areas. Columbus returned from his voyage to the New World in the latter part of the 15th century laden with new plants that ushered in an extended era of state-sponsored expeditions to gather and evaluate plant materials the world over. For most of that time, new crop varieties were largely treated as common property, shared freely among farmers and countries, and generating billions of dollars of benefits worldwide.

The era of free and unencumbered access to new crop varieties appears to be passing. This has implications beyond the movement and marketing of new crop varieties; it affects their creation as well. Scientific crop breeding, drawing on rediscovered Mendelian Laws of Heredity, began in earnest about a century ago. For many countries, varietal innovations continue to rely heavily on introduced germplasm, making the international spillovers of germplasm, breeding techniques, and know-how integral to these crop improvement efforts. While substantial germplasm (much in the form of landraces and other primary plant materials) flowed from poorer countries into the rich ones, so too did enhanced germplasm subsequently move back to the poorer parts of the world. This reverse flow appears to have accelerated as the Green Revolution took hold, beginning in the 1960s, as developing country farmers took up improved varieties in a big way, and as local

breeding efforts screened and adapted these varietal spillins to better deal with local agroecological realities and production constraints.

Throughout all these changes, crop improvement has been, and largely remains, a cumulative or sequential innovation process–new varieties build directly on the selection and breeding efforts of farmers and scientists of yesteryear. A new twist has come with the advent of modern biotechnology tools. The genetic makeup of new varieties is now altered by the "conventional or classical" genetic manipulation techniques practised formally by scientists for the past 100 years (and less formally by farmers for eons prior to that). It is also altered by bioengineered techniques involving the purposeful insertion of gene fragments into plants from other plants, or other organisms using genomic and transformation technologies developed within the past two decades.[1] Like the crop varieties themselves, the tools of crop manipulation are increasingly encumbered by intellectual property, making the future of crop improvement inextricably tied to the future of the biotechnologies increasingly used to manipulate them.

Whether these changing market, scientific, and intellectual property regimes will help or hinder efforts to develop and disseminate varietal technologies in the future, and especially the crop innovations required by developing countries, is an open question. In this paper we review and report newly compiled evidence on the research and, especially, the intellectual property landscapes concerning plant biotechnologies as a step toward resolving these questions.

Crop Biotechnology Creation

Crop biotechnologies are not necessarily used or protected where created. Here we investigate the location and structure of the relevant R&D sectors as a basis for analyzing the patterns of intellectual property rights in the resulting crop innovations and their uptake worldwide.

Research spending

In 1995 about half a trillion (nearly US$500 billion, 1993 prices) dollars was invested in all public and privately financed science worldwide–around 85% of it

[1]All crops are genetically modified, making the mnemonic "GMOs (genetically modified organisms)" misleading in ways that seem to have profoundly affected peoples' perceptions about the latest set of crop-improvement techniques. Among the continuum of genetic modification methods, for some purposes it is useful to distinguish between classically bred crops using techniques like hybridization that became commonplace among scientific breeders beginning a century ago, and varieties whose DNA has been manipulated with bioengineering techniques like the ballistic gun or agrobacterium mediated transformations of DNA that form the forefront of present crop improvement methods. Confounding efforts to neatly classify crop varieties, some modern varieties are conventionally bred but incorporate herbicide-tolerant genes identified using modern genomic methods.

conducted in rich countries (Pardey and Beintema, 2001). Agricultural research accounted for US$33 billion of this total or nearly 7% of all private and public spending on science.

The public share of agricultural investment was substantial, but is now flagging. Worldwide, public investments in agricultural research nearly doubled in inflation-adjusted terms over the past 20 years, from an estimated US$11.8 billion in 1976 to nearly US$22 billion in 1995. Yet for many parts of the world, growth in spending during the 1990s slowed dramatically. In the rich countries, public investment grew just 0.3% annually between 1991 and 1996 compared with 2.3% per year during the 1980s. In Africa, there was no growth at all. In Asia, the 4.4% annual growth figure compared with 7.5% the previous decade.

The distribution of spending on agricultural research has shifted as well. In the 1990s, for the first time, developing countries as a group spent more on public agricultural research than the industrial countries. Among the rich countries, US$10.2 billion in public spending was concentrated in just a handful of countries. In 1995 the United States, Japan, France, and Germany accounted for two-thirds of this public research, about the same as two decades before. Just three developing countries–China, India, and Brazil–spent 44% of the developing world's public agricultural research money in 1995, up from 35% in the mid 1970s.

By the mid 1990s about one-third of the US$33 billion total public and private agricultural research investment worldwide was private (Table 29.1). But little of this research takes place in developing countries. The overwhelming majority (US$10.8 billion, or 94% of the global total in 1995) is conducted in industrial countries, where private research is over half of all expenditures. In developing countries, the private share of research is just 5%, and public funds are still the major source of support.

Private agricultural research is displacing public research generally, and specifically in areas like commercial crop breeding for the seeds of crops with high commercial value. This tendency is especially pronounced in countries like the United States where private agricultural R&D was 90% of public spending in 1960, growing to 133% by 1996, the latest year for which comparable public-private data are available. Private investments, fueled by agricultural biotechnology research, gravitate to techniques that promise large markets, are protected by intellectual property rights, and are easily transferable across agroecologies. These included food processing and other postharvest technologies and chemical inputs including pesticides, herbicides, and fertilizers. Hence, while private research is much more geographically concentrated than public research, many of its fruits may be more easily transferred across borders and agroecological zones. Even so, private research is far less likely in products or methods with small markets, weak intellectual property protection, and limited transferability, precisely the situations in which most poor farmers are found.

Table 29.1: Private and Public Agricultural R&D Investments, circa 1995.

	Expenditures			Shares		
	Public	**Private**	**Total**	**Public**	**Private**	**Total**
	(million 1993 international dollars)			**(percent)**		
Developing countries	11,469	672	12,141	94.5	5.5	100
Industrial countries	10,215	10,829	21,044	48.5	51.5	100
Total	*21,692*	*11,511*	*33,204*	*65.3*	*34.7*	*100*

Source: Pardey and Beintema (2001).
Note: Drawing together estimates from various sources meant there were unavoidable discrepancies in what constitutes "private" and "public" research. For example, the available data for Asia includes nonprofit producer organizations as part of private research, whereas Pardey and Beintema opted to include research done by nonprofit agencies as part of public research in Latin America and elsewhere when possible.

Research intensities and stocks of knowledge

One way to gauge the commitment of agricultural research funds, public or private, is to compare them to national agricultural output, rather than measuring them in absolute terms. This relative measure captures the intensity of investment in agricultural research as a percentage of agricultural GDP, not just the amount of total research spending. In 1995, as a group, industrial countries spent US$5.43 on public and private agricultural R&D for every US$100 of agricultural output, compared with just 66 cents per hundred dollars of output for developing countries. The eight-fold difference in total research intensities illustrates the size of the technological gap in agriculture between rich and poor countries. Moreover, the situation is growing worse. The difference in public research intensity ratios was 3.5-fold in the 1970s, compared with 4.3-fold now (an even wider gap would have opened up if private spending was also factored in).

These trends may actually understate the scientific knowledge gap. Science is a cumulative endeavor, with a snowball effect. Innovations beget new ideas and further rounds of innovation or additions to the cumulative stock of knowledge. The sequential and cumulative nature of scientific progress and knowledge is starkly illustrated by crop improvement. It generally takes 7-10 years of breeding to develop a uniform, stable, and superior variety (with improved yield, grain quality, or other attributes). But breeders of today build on a base of knowledge built up by breeders of yesteryear. The cumulative nature of this process means that past discoveries and related research are an integral part of contemporary agricultural innovations. Conversely, the loss of a variety (or the details of the breeding histories that brought it about) means the loss of accumulated past research to the present stock of

knowledge. Providing adequate funding for research is thus only part of the science story. Putting in place the policies and practices to accumulate innovations and increase and preserve the stock of knowledge is an equally important and almost universally unappreciated foundation.[2]

Estimates of the stocks of scientific knowledge arising from public and private research conducted in the United States and sub-Saharan Africa have been developed by Pardey and Beintema (2001). Historical research spending (running from 1850 for the United States and 1900 for Africa and allowing for a gradual diminution of the effect of distant past R&D spending on money measures of the current stock of knowledge) was compared with the gross domestic agricultural product for 1995. The accumulated stock of knowledge in the United States was ten times more than the amount of agricultural output produced in that year. In other words, for every US$100 of agricultural output there existed a US$1000 stock of knowledge to draw upon. In Africa the stock of knowledge in 1995 was actually less than the value of African agricultural output. The ratio of the US knowledge stock relative to US agricultural output in 1995 was nearly 12 times higher than the corresponding amount for Africa. Stocks of knowledge measures provide a better basis for evaluating the industrial versus developing country capacities for actually carrying out crop biotechnologies. In fact, the overall differences may understate the effective gaps for this advanced area of agricultural R&D. These gaps also underscore the immensity, if not the outright impossibility, of playing "catch-up," in addition to the need to transfer knowledge across borders and continents.

Biotechnology trials

Absent meaningful data on "crop-related biotechnology research" spending, the only indication of the location of crop biotechnology research is data on the number of field trials conducted internationally.[3] Pardey and Beintema (2001) compiled data on the number of field trials conducted on bioengineered crops from 1987 through December 2000 grouped by the regions in the world where the trials were conducted

[2]Discoveries and data that are improperly documented or inaccessible (and so effectively exist only in the minds of the relevant researchers) are lost from the historical record when researchers retire from science. These "hidden" losses seem particularly prevalent in cash-strapped research agencies in the developing world, where inadequate and often irregular amounts of funding limit the functioning of libraries, data banks and genebanks, and hasten staff turnover. There can also be catastrophic losses, tied to the political instability that is a root cause of hunger. Civil strife and wars cause an exodus of scientific staff, or at least a flight from practising science.

[3]Precisely what is meant by "crop-related biotechnology research" is difficult to determine. "Biotechnology" can run the whole gamut from conventional breeding, through culturing methods, to genomic and bioengineering (including transgenic) techniques. In addition, and as discussed regarding the patent data reported below, many biotechnology techniques developed with spending directed to the health sciences, for example, have agricultural applications as well.

(Table 29.2).[4] According to these data, a total of 27 countries conducted trials on 14 different crops and 183 different "events."[5]

Eighty-four percent of the world's trials were conducted in rich countries; two-thirds of the total was in the United States and Canada alone. This points to a biotechnology-research gap between rich and poor countries that is even more pronounced than the gap in overall agricultural R&D spending (wherein 64% of global agricultural R&D was conducted in rich counties). Two fundamental factors may account for much of the marked spatial asymmetry in agricultural biotechnology research: specifically, who conducts the research, and the nature of the science itself. First, as indicated in Table 29.2, most of these biotechnology trials are conducted by private firms and most of the world's private agricultural R&D (about 94%, Table 29.2) takes place in rich countries. Second, this type of cutting-edge research requires access to highly skilled scientists, well functioning scientific infrastructure that provides ready access to reagents and a myriad of laboratory equipment and supplies, along with technical information, and the appropriately trained support staff to help carry out the research. Although most of the trials are conducted by private firms, the sophistication of the research involved and its pace of change mean that "applied" aspects of the biosciences are likely to receive significant spillovers from ongoing basic research, and from accumulated stocks of scientific knowledge arising from past research. These elements are much more readily supplied in rich than in poor countries. Indeed, it is the localized spillovers from university research (often involving tacit knowledge embodied in the scientific and technically trained people that form part of university communities) that influences the location of industrial research and development (R&D) (Adams, 2001; see also Graff *et al.*, 2003).

[4]As indicators of the level of bioengineering research effort, these data must be taken with a grain of salt. To meaningfully assess the distribution of transgenic crops being tested in the ground, one would like the notion of "field trial" to be standardized across countries. One option is to count each location as a separate instance. But in the United States, for example, a "location" can have many sites. For example, test 01-024-26n in the APHIS database contains Pennsylvania as one location, but there are 313 sites comprising a total of 744 hectares. Likewise, Canada lists field trials conducted at multiple sites within a province as one field trial, but it is not clear if all the data for all the other countries are reported similarly.

[5]An event involves the insertion of a specific gene in a particular crop, resulting in the expression of a trait in that crop. For example, insertion of the Bt cry1(c) protein producing gene into a particular cotton variety is considered an event.

Table 29.2. Field Trials of Bioengineered Crops by Regions of the World.

	Number of Approved Events/crops[a]			Field Trials[a]			
				Number of		Share of	
	Countries	Events	Crops	Countries	Trials	Global total	Private in-country total
						(percentage)	
Industrial Countries	19	160	14	20	9,701	84.2	na
United States	1	49	14	1	6,337	55	83.4
Canada	1	49	4	1	1,233	10.7	63.9
All others	17	62	5	18	2,131	18.5	na
Developing Countries	8	23	4	19	1,822	15.8	na
Argentina	1	7	3	1	393	3.4	90.1
China	1	5	4	1	45	0.4	na
All others	6	11	3	17	1,384	12	na
Total	*27*	*183*	*14*	*39*	*11,523*	*100*	*na*

Source: Pardey and Beintema (2001).
Note: na stands for not available.
[a]Data through to December 2000 where available. For the United States and Canada, and perhaps other countries, a single "trial" may consist of tests conducted at multiple (maybe many) different sites.

An Economic Primer on Intellectual Property Rights

R&D, like almost all other aspects of life, is an economic activity. Who pays for the research, who performs what research where, and who gains and loses (and by how much) as a consequence are all influenced by economic incentives. The degree to which innovators can appropriate the fruits of their endeavors lies at the heart of the incentives to invest, giving rise to pervasive policies worldwide to assign property rights to innovations in an effort to better align private incentives with social interests.

The conventional rationale for protecting intellectual property by patents or other means is to provide some proprietary or "monopoly" rights to an invention–albeit circumscribed and exclusionary in nature–in exchange for public disclosure of the details of the invention (Nordhaus, 1969). What is disclosed may be useful for further innovation. But the monopoly right also encourages invention

directly, and the social value of the right tends to include surplus above the private value. Thus, the (private and social) benefits of patents include wide diffusion of the creation of aspects of new or advanced technologies. The costs are transitory (for the life of a patent) and entail higher-than-otherwise prices or constrained choices of innovations subject to some monopolistic behavior. However, this conventional, static, one-off view of invention does not fully reflect the dynamic nature of a large part of R&D.

Much technological change comes in the form of cumulative innovation processes, whereby the fruits of innovation frequently materialize as the embodiment of a sequence of prior innovations. While strong patent protection may stimulate the earlier-than-otherwise development of a research tool, it can also delay or deter follow-on innovation due to the transaction costs of negotiating a license or merger and the ability to prevent competitors from introducing similar technology (Merges and Nelson, 1990, Heller and Eisenberg, 1998). Thus the dynamic cost of a patent within a cumulative innovation scheme–which includes the accumulated costs of delayed follow-on inventions–is an important policy consideration that is often neglected when counting the conventional (i.e., static) social cost of a patent (Koo and Wright, 2002).

A special case of cumulative innovation involves the development of a research tool, that is a product or process whose only value is as an input to follow-on innovations. In agricultural biotechnology, a research tool can be a patent on a DNA sequence modified to enhance the expression of a trait such as insect-resistance, while the follow-on innovation may be a new transgenic variety of cotton. Since the patentee of a research tool can capture revenue only through direct production of the follow-on innovations, efficient compensation of the patentee, through licensing, joint ventures, or other means, is critical in providing the incentive to innovate research tools. In addition, these efficient mechanisms also reduce the transaction costs incurred by those contracting for use of the rights, thereby encouraging the utilization of research tools by follow-on innovators.

One way of reducing dynamic costs and encouraging technology transactions is to clarify property rights. The Bayh-Dole Act of 1980 and subsequent legislation, which allowed US universities, other nonprofit institutions, and government labs to patent and exclusively license federally funded inventions, was intended to achieve this purpose. Firms are often unwilling to invest significantly in developing and disseminating innovations lacking clearly defined property rights. This point was clearly captured by the 1945 Report of the US House of Representatives, which stated that "… what is available for exploitation by everyone is undertaken by no one (cited from Jaffe, 2000, p.534)." The main objective of the Bayh-Dole Act is to foster markets for the transfer of technology, and there is some evidence the Act has achieved these aims (Jensen and Thursby, 2001). However, the Bayh-Dole Act is most effective when inventions require heavy expenditure in downstream technology and product development, which is not the case for all technologies. In addition, some have argued that the Act may actually constrain and delay the flow of

fundamental scientific knowledge (as "prior art" concerns impede open scientific discourse through seminars and the professional literature), and shift the emphasis of university research from fundamental basic research toward more applied research. The latter is potentially more rewarding financially for the university (or its research faculty), but not necessarily for society as a whole over the longer run (Mazzoleni and Nelson, 1998).

The impact of a patent system also depends on the type of technology itself. Agriculture seeds have special attributes, most significantly their almost costlessly reproducible nature, which merit special attention. Under plant variety protection schemes, farmers may legally save and reuse (and sometimes sell) seeds in following seasons, so that seed firms are faced with only the residual demand for their seeds in subsequent seasons. This problem, together with the difficulty of monitoring and enforcing property rights to seed, makes its legal protection less valuable than other forms of protection on other products. Private seed markets have responded to the appropriability problem by developing hybrid varieties or pursuing genetic use restriction technologies (GURTs), both of which prevent seeds from effectively reproducing, a form of "biological" rather than legal property protection.

What evidence is there that intellectual property rights (IPRs) stimulate inventive activity? Although there are no readily measurable markets for IPRs in which the benefits and costs of patents, for example, can be easily evaluated, a few studies have sought to measure the overall inventive effects of patents. Findings from survey studies suggest that innovators rely primarily on other means (like trade secrets or first-mover advantages) rather than patent protection to appropriate the returns from their innovative investment, with the exception of pharmaceuticals (Levin *et al.,* 1987; Cohen *et al.,* 2000). Some have estimated the private value of patent protection using patent data, concluding that the distribution of patent rights values is sharply skewed, with most of the value concentrated in a small number of patents (Lanjouw *et al.,* 1998). Using European patent renewal data, Schankerman (1998) estimated that the private value of patent protection was about 15-25% of the related R&D expenditure, suggesting a small impact of patent rights on innovative behavior.

Most empirical studies, all using US data, have generally found weak or indeterminate empirical evidence to suggest that plant breeders' rights are effective in stimulating investments in varietal improvement research (Perrin *et al.,* 1983; Knudson and Pray, 1991; Alston and Venner, 2002). Some point out that plant variety protection does not provide patent-like ex ante investment incentives, nor generate substantial ex post licensing and enforcement activity (Janis and Kesan, 2002). Alston and Venner (2002) found that varietal rights for wheat in the United States had little measurable impact on the rate of technical change in that crop, and may simply have served as a marketing tool.

Given evidence of the general lack of appropriability from patent or plant variety protection, why do innovators continue to apply for intellectual property protection? Even accepting the claims that practising patents may not be the primary

means by which large firms recoup their R&D investments, it can still be an important incentive mechanism for smaller new entrants and the venture capital firms that often fund them. Patent portfolios may be critical to obtaining venture capital or to maintaining control of the technology while downstream innovation is pursued or production and sales capabilities are established (Kitch, 1977; Mazzoleni and Nelson, 1998). In addition, firms (large and small) use patents to block products of their competitors, and as bargaining chips when negotiating cross-licensing agreements, as is the case of the semiconductor industry (Hall and Ziedonis, 2001). Strategic patenting behavior that relies on larger patent portfolios is consistent with rising rates of patenting and high patent-to-R&D spending ratios, even absent any perceived increase in the appropriable value of patents. For some developing countries with newly introduced plant variety rights, such as China, a surge in plant variety protection applications may be explained by an over-optimistic view of the prospective value of varietal rights. The current size of their seed market and the cost and effectiveness of protection do not seem to economically justify the extent of protection presently being sought (Koo *et al.*, 2003).

Crop Biotechnologies as Property

Creating new crop biotechnologies is one thing, protecting the intellectual property embodied in them is an altogether (but not unrelated) other thing, with its own set of economic costs and benefits. Notwithstanding the incentive-to-innovate arguments broached earlier, one view is that intellectual property rights over plant biotechnologies in rich and poor countries leads to a lock-out phenomenon. The growth in intellectual property is restricting access to proprietary research results in ways that curtail the freedom to operate for research conducted in or on behalf of poor countries, to the detriment of developing country food-security prospects. This view is commonly held, absent evidence on the international pattern of intellectual property protection, or a clear understanding of the effect this has on the rate and direction of inventive activity, the use to which these inventions are put, and the trade in agricultural products arising from this research. What follows is a first pass at describing the IPR evidence for plant biotechnologies internationally.

Plant variety protection

Global trends

The pattern of applications for plant breeders' rights (PBRs) since 1971 for 37 countries grouped into four per-capita-income classes is shown in Table 29.3. Nearly 138,000 PBR applications have been lodged worldwide since 1971.[6] During the 1970s and 1980s, rich countries accounted for 92-96% of the total applications. Their share throughout the 1990s declined to an average 75% in 2001-02. PBR applications filed in upper-middle-income countries–including Argentina, Chile, Czech Republic, Hungary, Poland, Slovakia, South Africa, and Uruguay–grew steadily since the early 1970s, while reported PBR applications in lower-middle-income countries–that now includes Brazil, Bulgaria, China, Colombia, Romania, the Russian Republic, and Ukraine–began increasing a decade later.

The shifting geographical pattern of plant varietal protection arises for several reasons. The growth in the total number of applications is the result of an increase in the rate of applications per country per year. Most high-income countries had PBR legislation in place for most of the period reported here, while in middle-income countries there was a rapid growth in the number of countries offering plant breeders rights (2 countries in 1971; 5 in 1985; 8 in 1990; and 15 in 2002).[7] Increasing rates of protection may reflect legal-cum-economic as well as institutional factors. One would expect applications to increase over time as awareness of the existence and effectiveness of PBRs in a particular country increased and as the economic costs of applying for and evaluating applications declined with improved bureaucratic procedures.[8]

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[6]Some applications were lodged before 1970, but the number is small (less than 3%) compared with the totals reported in Table 29.3.

[7]Plant breeders' rights have been available in many rich countries for at least the past 30 years. Germany, for example, has issued plant breeders rights since at least the 1950s, and likewise for a few other European countries. The United States began issuing plant variety protection certificates (PVPCs) in 1971 for sexually reproduced plants: asexually reproduced plants (like grape vines, fruit trees, strawberries, and ornamentals that are propagated through cuttings and graftings) have had recourse to intellectual property protection since 1930 when the Plant Patent Act was passed. Many middle-income counties passed PVP legislation during the 1990s in compliance with their sui generis obligations to offer the intellectual property rights over plant varieties enshrined in article 27(3)b of the 1995 Trade-Related Aspects of Intellectual Property (TRIPs) agreement in the World Trade Organization (WTO). An indication of the geographical extent of plant breeders' rights is the listing of member countries of the International Union for the Protection of New Varieties of Plants (UPOV). At its inception in 1961, UPOV had five member countries (Belgium, France, Germany, Italy, and Netherlands, all of them high-income countries), growing to 20 countries by the end of 1992, then increasing rapidly to 53 countries–21 high income, 27 middle income and 5 low income–as of September 2003. Notably, under the TRIPs agreement, the "least developed" countries (a WTO designation) are exempt from complying with article 27(3)b until 2005.

[8]In addition, some countries have expanded the scope of crops eligible for protection over time. In China, for instance, a total of 10 species were eligible for protection in September 1999, growing to 30 species by March 2002 (including 5 major cereals, 2 oil crops, 2 roots and tubers, 10 vegetables and fruits, and 11 flowers and grasses but excluding cotton).

Table 29.3. Plant Breeders Rights Applications—Countries Grouped by Per Capita Income, 1971-02.

Income group	1971-75	1976-80	1981-85	1986-90	1991-95	1996-00	2001-02	Total
Number of applications	**(counts)**							
High income country (21)	3,015	5,794	10,871	20,433	31,361	34,287	13,257	119,018
Upper middle income country (8)	66	206	402	1,658	3,555	5,228	2,369	13,484
Lower middle income country (7)	25	34	57	58	158	2,980	2,121	5,433
Low income country (1)	–	–	–	–	–	23	–	23
Total	***3,106***	***6,034***	***11,330***	***22,149***	***35,074***	***42,518***	***17,747***	***137,958***
Application rates	**(counts per year)**							
High income country (21)	87	102	167	299	343	327	126	1,452
Upper middle income country (8)	8	7	20	61	91	131	59	377
Lower middle income country (7)	5	6	11	9	11	113	61	215
Low income country (1)	–	–	–	–	–	5	–	5
Total	***100***	***115***	***198***	***369***	***445***	***576***	***246***	***2,049***
Shares of total	**(percentage)**							
High income country (21)	97	96	96	92	89	81	75	86
Upper middle income country (8)	2	3	4	7	10	12	13	10
Lower middle income country (7)	1	1	1	0	0	7	12	4
Low income country (1)	0	0	0	0	0	0	0	0
Total	***100***	***101***	***99***	***99***	***100***	***100***	***100***	***100***

Source: Authors compiled from data obtained from UPOV (2003b), Koo *et al.,* (2003) for China; Koo *et al.,* (2004) for Brazil; and US Plant Variety Protection Office's public access database for the United States.

[a]Bracketed numbers indicate number of countries in each income class. Countries are classified into income classes according to World Bank (2004) criteria. Countries with 2003 per capita gross national incomes greater than US$9386 are designated high income; US$3036-9385 are upper-middle income; US$766-3035 are lower-middle income; and less than US$765 are low income.

Notably, the number of PBRs sought in low-income countries is negligible: only 23 applications from Kyrgyzstan. The principal proximate cause of this situation is the lack of rights on offer in poor countries. More fundamentally, it reflects a range of economic influences regarding the costs and benefits of securing breeders rights in a particular jurisdiction.

To capture this cost-benefit calculus, Koo *et al.,* (2003) use an option value model to characterize the crop breeders' decision to apply for and retain varietal protection. Although the costs of gaining and securing plant variety protection are known with reasonable surety, the sequence of future returns from a varietal right is highly uncertain for many reasons. There are uncertainties about the size of the appropriable seed market for a given crop, the probability of commercial success of the protected variety, and the extent of enforcement of assigned property rights. Where required, breeders make periodic (often annual) renewal decisions, preserving the right to pay renewal fees and exercise their exclusionary rights in future periods. Thus applying for, and subsequently renewing, PVP rights is a way of reserving the rights to potential future revenues, even if revenues in the short term are negligible. Thus the expected value of holding plant variety rights consists of the current returns captured from the coming year, and the option to renew the right in the subsequent year.

Foreign PBR applications

The UPOV (2003a) data on varietal rights applications allows us to distinguish between domestic and foreign applicants. Overall, 34% (17,529 of a total of 51,258) of the applications filed in 50 UPOV member countries during 1998-02 were lodged by foreigners (Table 29.4). This substantial fraction of foreign applications indicates extensive potential spillovers of varietal improvement research done in one locale on seed market and production developments elsewhere in the world. The intensity of foreign participation in domestic varietal rights markets differs markedly. Looking regionally, 31% of the applications in high-income countries were lodged by foreigners, 65% in upper middle-income countries, 25% of in lower-middle income countries, and 38% in low-income countries. The country-by-country participation of foreigners is even more variable. For example, the share of foreign applications is 85% in Switzerland and Canada, 42% in the United States, 37% in the United Kingdom, 24% in Japan, 16% in the Netherlands and Germany, and 11% in France.

Table 29.4. Share of plant breeder rights applications lodged by foreigners, 1998-2002.

Economies	Residents	Nonresidents	Total
	(number of applications)		
High income economies (23)	26,893	12,186	39,079
Upper middle income economies (11)	1,945	3,638	5,583
Lower middle income economies (12)	4,592	1,517	6,109
Low income economies (4)	299	188	487
Total (50)	**33,729**	**17,529**	**51,258**

Source: UPOV (2003a).
Notes: See table 29.3 for country income classification criteria.
[a]Bracketed figures indicate number of countries included in the data.

European and United States trends

Worldwide, seed sales are estimated to be US$30 billion annually (ISF, 2003). Although the economic value of seed markets within the European Union (about US$5.2 billion in total) are a little less than US seed sales (US$5.7 billion), there have been three times more PBR applications since 1971 lodged throughout Europe than related applications in the United States (Table 29.5). Much of the difference may stem from multiple applications for the same variety among national jurisdictions in Europe, whereas only one application is required per variety in the United States. Part of the difference may arise from the different forms of varietal protection on offer in Europe (PBRs) versus the United States (plant patents and plant variety protection certificates, as well as utility patents). About 5% of all the plant breeders and related patent applications in the United States are for utility patents, of which 55% pertain to corn and 40% to soybeans.

Four countries–Netherlands, France, Germany, and the United Kingdom–account for most of the European applications. Adding applications lodged with the Community Plant Variety Office (CPVO) to those filed nationally, the Netherlands accounted for 35% of the European total, France 22%, Germany 16%, and the United Kingdom 8%.[9] The number of PBR applications filed with the CPVO has increased over time, offsetting declines in the number of applications

[9]Prior to April 27, 1995, when the Community Plant Variety Office (CPVO) was established, a breeder seeking protection for a variety throughout the European Union was required to submit an application to each of the member states. Now with a single application to CPVO, a breeder can be granted varietal protection rights throughout the European Union. This European-wide system–CPVO members currently include Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, and the United Kingdom–operates in parallel with respective national systems, although the owner of a variety cannot simultaneously exploit both a community plant

lodged with national protection offices. In 1996, there were 1385 applications lodged with the CPVO and a total of 2766 applications made to individual national systems. By 2000, almost equal numbers of PBR claims were filed with the CPVO and the respective national offices (about 2000 applications each), and in 2001 CPVO applications (2158) exceeded those filed with national offices (1864).

Regarding the types of crops for which varietal protection is sought, ornamental crops account for more than half the total applications in both the United States and Europe (Figure 29.1). In the United States, cereal crops (such as wheat and corn), as well as oil and fibers, and fruit crops each make up more than 10% of the total number of applications since 1970. Ornamentals and fruits are usually protected by plant patents, whereas cereal, oil and fiber crops, and vegetables are usually protected by plant variety rights. In Europe, cereals account for more than one-quarter of the total PBR applications, followed by vegetable (10%), oil and fiber crop (5%), and fruit (5%).

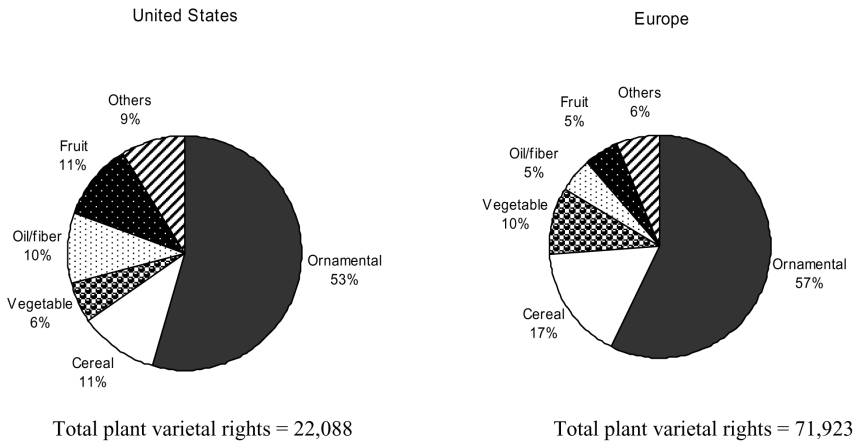


Figure 29.1. Plant Breeders' Rights stratified by crop categories.
Notes: United States data includes total number of plant patents granted from 1930 to 2003 and plant variety protection applications from 1970 to 2003. Data for European Union includes plant breeders' rights applications to national plant variety offices from or near their inception dates (1942 for Netherlands, 1955 for Germany, 1970s and 1980s for most other countries) to 2003 and the CPVO from 1995 to 2003.

variety right (CPVR) and a national plant breeders right in relation to that variety. Individuals or companies from member states of UPOV, but not a member of the European Union, can also apply, provided that an agent domiciled in the Community has been nominated. The duration of CPVR protection is 25 years for most crops, and 30 years for potato, vine, and tree varieties.

Table 29.5. Plant-Related IP Applications in the European Union and the United States.

Income group	Before 1970	1971-75	1976-80	1981-85	1986-90	1991-95	1996-00	2001-02	Total
					(counts)				
European Uniona	**598**	**843**	**4,369**	**6,376**	**13,254**	**20,290**	**19,232**	**7,472**	**72,432**
Netherlands	140	213	518	1,369	4,252	6,838	4,278	1,386	18,994
France	–	–	2,151	2,046	3,206	3,395	2,326	686	13,810
Germany	212	244	436	1,007	2,275	3,042	1,306	472	8,994
UK	2	6	8	6	500	2,365	1,334	359	4,580
Others	244	380	1,256	1,946	3,021	4650	1344	188	12,029
CPVO[b]	–	–	–	–	–	–	8,644	4,381	13,025
United States[a]	**3,495**	**1,313**	**1,587**	**2,045**	**3,150**	**3,754**	**6,539**	**2,013**	**23,896**
Plant Variety Protection	–	600	614	934	1,228	1,505	1,943	562	7,386
Plant Patents	3,495	713	973	1,105	1,883	2,089	3,666	1,346	15,270
Utility Patents[c]				6	39	160	930	105	1,240

Source: Compiled by authors from commissioned data obtained from the US Patent and Trademark Office, Office of Electronic Information Products for US plant and utility patents; the US Plant Variety Protection Office's public access database for the US plant variety protection; and UPOV (2003b) and CPVO (2003) for data of European Union countries and CVPO series, respectively.

[a]European Union aggregate includes applications for plant breeders' rights in 13 European countries. US aggregate of plant and utility patents granted and plant variety protection certificate applications.

[b]CPVO (Community Plant Variety Office) members currently include Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, and the United Kingdom. Individuals or companies from member states of UPOV, but not a member of the European Union, can also apply, provided that an agent domiciled in the Community has been nominated (See CPVO (2002) for further details). Since it was first implemented in 1995, around 35% of these applications are lodged from the Netherlands, 16% from Germany, 14% from France, 19% from elsewhere in the European Union, and 16% from outside the European Union.

[c]Preliminary tabulation by authors based on patent-by-patent scrutiny of the US patent database to identify patents with claims that encompass plant varieties

Biotechnology patenting patterns

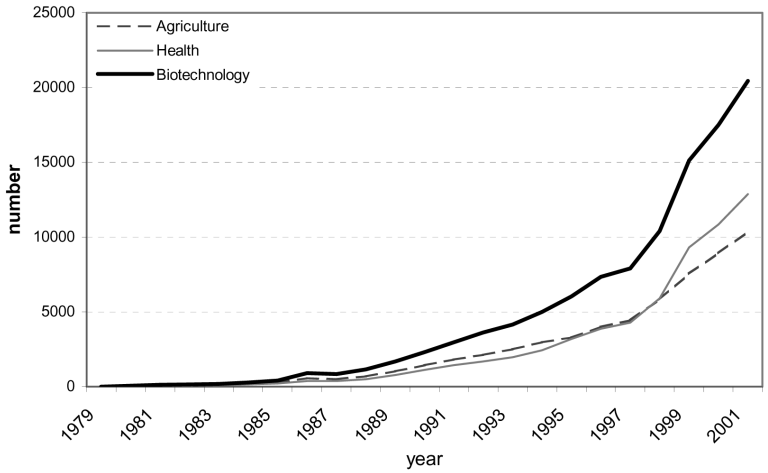
An initial foray into examining the international dimensions of patent activity in biotechnology and specific sectors, such as agriculture and health, is presented in Figure 29.2. Numbers of patent applications submitted to the World Intellectual Property Organization (WIPO) under the Patent Cooperation Treaty (PCT) (Figure 29.2b) and patents granted by the European Patent Office (EPO) (Figure 29.2b) are plotted against the year published. For this analysis, patent documents were selected on the basis of the International Patent Classification (IPC) scheme used by the patent offices. Data were obtained for documents satisfying criteria for "biotechnology" and further subdivided into "agricultural biotechnology" and "health biotechnology."[10] The numbers of the two subdivisions add to more than for biotechnology as some documents fit into both categories. While initially agricultural biotechnology patent documents exceeded health-related documents both at EPO and WIPO, the situation reversed in 1999. Furthermore, the spectacular rise in patent filings in the late 1980s and through the 1990s appears to be leveling off.

The data presented here contrast with recently reported analyses of Graff *et al.*, (2003), who noted drops in patent grants in plant biotechnology at the EPO after peaking in 1994-95. The differences may be due to disparities in the definition of plant or agricultural biotechnology. Their definition comprises a description of the scope of technologies, such as genetic engineering of plants, plant genes, and plant breeding methods, covering a small subset of IPC codes and specific technology keywords. In contrast, our definition encompasses broader aspects of plant biotechnology, including genetic modification of plants, biocides, organic or enzymic-based methods for preservation of foods, microbiological treatment of water and soil, compositions containing microorganisms or enzymes, and processes using microorganisms or enzymes. The definitional differences are highlighted by the order of magnitude difference in the number of documents that satisfy the criteria. For example, in 2000, we obtained 8859 PCT patent filings and 5097 EP patent grants for inventions concerning agricultural biotechnology, compared with around 625 PCT applications and 50 EP patent grants for the narrower area of "plant biotechnology" reported by Graff *et al.*, (2003).

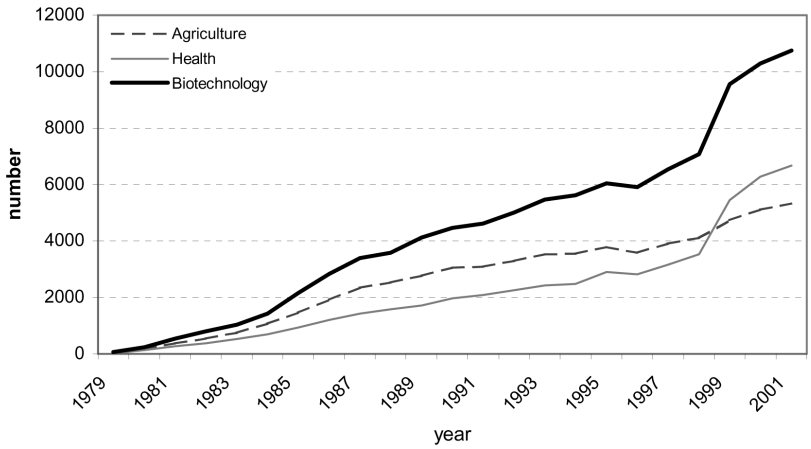
The percentage of PCT applications in agricultural biotechnology has been on the rise. In 1985, agricultural biotechnology applications were 4.0% of the total submitted. By 1990, they were 7.5% of the total, and in 2000 had risen to 9.7% of the total. In 2000, agbiotech patents granted in EPO were 18.5% of the total granted. Clearly further examination of patent activity with an eye to the commercial and public good consequences encompassing the changing geographical and institutional

[10]For this work, "biotechnology" refers to "the application of science and technology to living organisms as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services," a definition used by the OECD (see "Statistical definition of biotechnology" 12 June 2002 in the Biotechnology, Statistics section of www.oecd.org).

origins of biotechnology innovations on a global scale, and their spillovers or transfer to other countries, will be sensitive to the patents included in the source set of documents.



(a) PCT applications



(b) European patents grants

Figure 29.2. Biotechnology patents.
Source: Compiled by authors from CAMBIA-IP Resource database.

Crop Biotechnology Use

The evidence on the worldwide dissemination of contemporary, bioengineered crop technologies is usefully viewed in the context of the diffusion of the classically bred crop varieties that preceded them.

Classically bred crop varieties

Worldwide, around 95% of major cereal production gains during the past 40 years came from increased yields, which have more than doubled since 1961 (Runge *et al.*, 2003). Increasing yields result from increased use of inputs such as agricultural chemicals (including fertilizers, herbicides, and pesticides), irrigation water, and improved crop varieties. In the industrial world at least, the growth in crop yields began picking up pace several hundred years ago. Looking in detail at developments in the US wheat varieties since 1800, Olmstead and Rhode (2002), for example, estimated that roughly one-half of the US growth in labor productivity in that crop between 1839 and 1909 was attributable to biological innovations. Pardey *et al.*, (1996) showed that wheat varietal change in the United States accelerated during the 20th century–an average of 5.1 commercially successful wheat varieties were introduced each year from 1901 to 1970, and the rate jumped to 29.6 varieties per year during the period 1971 to 1990. Moreover, the creation of these new varieties continued to rely heavily on foreign germplasm. By the early 1990s, one-fifth of the total US wheat hectarage and virtually all the spring-wheat cropped in California were sown to varieties with CIMMYT ancestry.[11]

There are still long lags between committing R&D dollars and realizing the returns on that investment. Even in the United States it took decades to build up the genetic resource base and train and deploy the scientists skilled in classical genetic manipulation techniques before reaping the really big dividends during the latter half of the 20th century. In the developing world, scientific crop breeding lagged well behind. Beginning in the 1950s and 1960s, improved varieties became increasingly available to farmers and yields rose: wheat went from 1 ton per hectare or less in China and India in the mid 1960s to over 2.5 tons in India, and almost 4 tons in China, by the late 1990s. The rapid spread of modern rice, wheat, and maize varieties throughout the developing world is shown in Table 29.6. Asia embraced these new varieties most rapidly, while adoption lagged in sub-Saharan Africa. A striking feature of these data, however, is the limited uptake of scientifically bred crop varieties throughout most developing countries as late as 1970. When virtually all the

[11]CIMMYT is the Spanish acronym for the International Maize and Wheat Improvement Center based in El Batãn, Mexico. Pardey *et al.*, (1996) estimated that the improved genetic makeup of wheat varieties between 1970 and 1993 was worth almost US$43 billion (1993 prices) to the United States–equivalent to 10.6 % of the present value of wheat production during this period–and that up to US$13.6 billion of that total benefit was attributable to varietal spillins from CIMMYT alone.

cropped hectarage in rich countries was sown to scientifically bred rice and wheat varieties, less than one-third of the developing world's rice hectarage and just one-fifth of its wheat hectarage were planted to modern forms of these crops.

For these three food staples much of the crop improvement research involved publicly funded and conducted research. The big innovation of the 1960s and 1970s for rice and wheat was the development and release of increasing numbers of semi-dwarf varieties by national and international research agencies bred using plant material and crop transformation techniques that were entirely public domain. Almost all the resulting improved varieties were made available without personal or corporate intellectual property rights. The public sector performed most of the research, and in few jurisdictions were IPRs over the varieties themselves or the techniques used to transform them even a legal option at that time.

For corn the story is different. While publicly bred varieties were, and remain, a feature of this crop, the private sector presence is much more pronounced. Hybrid corn technologies that took off in the United States in the 1930s (and later elsewhere) offered significant protection for the intellectual property embodied in them. This made it possible for breeders to appropriate a larger share of varietal benefits than was possible for the self-replicating forms of varietal transformations featured in rice and wheat.[12] For hybrid corn varieties, as long as the in-bred lines were kept secret (and laws were in place in the United States and elsewhere to help preserve these trade secrets), the cost of imitation was prohibitively large enabling inventors to appropriate significant shares of the benefits stemming from their efforts.

The developing country uptake of modern maize varieties has also been substantial as shown in Table 25.6, but less extensive than the move to improved forms of rice and wheat worldwide. This could partly be due to the greater proprietary (and private sector) nature of maize varietal changes, but a whole host of other influences could be operative as well. About 86% of the improved hectarage worldwide is sown to hybrids, the rest to open pollinated varieties.

[12]Hybrid technologies were also pursued for rice and wheat but less extensively so. Knudson and Ruttan (1988) document efforts to develop hybrid wheats in the United States. Hybrid rice is grown extensively in China, beginning in the mid 1960s. Since then, the area under hybrid rice has increased steadily to about 23% in 1981 and 61% in 2001 (Fan *et al.*, 2003). Notably, profit potentials were not a contributing factor to the development of this technology in China where the research was a government undertaking.

Table 29.6. Share of area planted to modern varieties of rice, wheat, and maize.

	Rice			Wheat				Maize	
Regions	**1970**	**1983**	**1991**	**1970**	**1977**	**1990**	**1997**	**1992**	**1996**
	(percentage of area planted)								
Sub-Saharan Africa	4	5	n.a.	5	22	52	66	37	46
West Asia/North Africa	0	11	n.a.	5	18	42	66	26	n.a.
Asia (excluding China)	12	48	67	42	69	88	93	42	64
China	77	95	100	n.a.	n.a.	70	79	79	99
Latin America	4	28	58	11	24	82	90	49	45
All developing countries	30	59	74	20	41	70	81	58	62

Source: For rice and wheat, Runge *et al.,* (2003) based on data from Byerlee and Moya (1993), Byerlee (1996), Heisey *et al.,* (1999). For maize, Morris (1998, 2002).
Note: n.a. indicates not available. Modern varieties of rice and wheat refer mainly to semi-dwarf varieties; for maize it includes hybrid and improved open pollinated varieties.

Varietal spillovers

While the agroecological specificities of much agricultural R&D–and especially many crop biotechnologies–limits the geographic scope of agricultural innovations, there is overwhelming evidence that spatial spillovers of technologies have played a pivotal part in productivity improvements worldwide. In reviewing the economic studies of this phenomenon, Alston (2002) concluded that interstate or international R&D spillovers might account for half or more of the total measured productivity growth.

Spillovers of crop varietal technologies have flowed in all sorts of directions. Pardey *et al.*, (1996) looked at the spillins to the United States of varietal improvement research done at the international agricultural research centers, specifically the International Maize and Wheat Improvement Center (CIMMYT) in Mexico and the International Rice Research Institute (IRRI) in the Philippines. They estimated that the US economy gained at least US$3.4 billion and up to US$14.6 billion–depending on the benefit attribution methods deployed–from 1970 to 1993 from the use of improved wheat varieties developed by CIMMYT. In the same 23-year period, they found that the U.S. economy realized at least US$30 million and up to US$1 billion through the use of rice varieties developed by IRRI.

Pardey *et al.*, (2004) quantified the benefits from crop improvement research in Brazil, and attributed them to the Brazilian National Agricultural Research Agency (Embrapa), other public and private agencies operating in Brazil, and spillovers from

the Consultative Group on International Agricultural Research (CGIAR) and the United States. They found that 64% of the total benefits from varietal improvement for upland rice in Brazil (which had a present value of US$1683 million in 1999 dollars over 1984-03), were from non-Embrapa sources. Likewise, 67% of the total benefits from varietal improvement research for edible beans (which had a present value of US$677 million in 1999 dollars over 1985-03) came from non-Embrapa sources, mostly within Brazil. However, 77% of the total benefits from varietal improvement research for soybeans (which had a present value of US$12,473 million in 1999 dollars over 1981-03) was due to non-Embrapa sources, with 22% of the benefits attributable to spillins from the United States.

Bioengineered crop varieties

Where the crop varieties and bioengineered traits embodied in them perform well and have been given approval for commercial use, the rate of uptake has been rapid (although contrary to some claims, not entirely unprecedented, even for biological innovations used in agriculture).[13] James (2002) estimates that 58.7 million hectares were planted to bioengineered crops worldwide in 2002, an increase from 52.6 million hectares in the previous year and well up on the 2.8 million hectares planted in 1996.[14]

Despite this growth, the geographical, crop, and technological scope of bioengineered crops is still small. In 2002, the preponderance of the area under these crops consisted of bioengineered soybean (62% of the total bioengineered cropping area sown to this crop): 21% of the area was sown to bioengineered maize, 12% to cotton, and 5% to canola. Just four countries accounted for 99% of the global total in 2002 (Figure 29.3). Two-thirds of this global total was planted in the United States, 22% in Argentina, 6% in Canada, and 3% in China. Two traits dominate the picture–herbicide tolerance (mainly in soybeans and canola) and insect tolerance (mainly in corn and cotton)–with some limited use of bioengineered viral resistance in papaya and squash.

The developing country share of global bioengineered crop area has grown (Figure 29.3): from 14% of the world total in 1997 to about 27% in 2002. Notably, it is plantings in just four countries–soybeans in Argentina, and cotton in China, South Africa, and for the first time in 2002, India–that accounts for the lion's share of the developing country bioengineered hectarage. Finding bioengineered traits that deal successfully with local production constraints is one thing, expressing them in

[13]Griliches (1957) studied the uptake of hybrid corn technologies in the United Sates and showed that Iowa, for example, went from 0 to 50% of the state's corn hectarage sown to hybrid varieties in just six years (1932-38), reaching 90% by 1940.

[14]The Flavr-SavrTM tomato, genetically engineered to delay softening so the tomato could ripen on the vine and retain its "fresh picked" flavor was the first bioengineered crop to be grown commercially (in 1994).

specific crop varieties that compete well locally against landraces and conventionally bred varieties of the same crop (absent the bioengineered trait) is an altogether different thing. Not surprisingly, the bioengineered traits are being grown in developing country areas that are agroecologically similar to the rich countries for which the traits were first developed, and in most cases involve the identical crop varieties.[15] This is precisely where the spillover costs are smallest (consisting mainly of local screening and regulatory approval costs along with the costs of marketing the technology). Therefore, disseminating these particular bioengineered crop varieties involves only adaptive or imitative technology development costs beyond the initial discovery costs–a much smaller cost than inventing entirely new bioengineered traits and successfully expressing those traits in locally superior varieties of locally important crops.

The site-specificity of many agricultural biotechnologies arises from agroecological conditions, which define the size of the relevant market in a way that is less common in other industrial R&D. As Alston and Pardey (1999) described, one way to think of this is in terms of the unit costs of making local research results applicable to other locations (for example by adaptive research), which must be added to the local research costs. Such costs grow with the size of the market.[16] Economies of size, scale, and scope in research mean that unit costs fall with size of the R&D enterprise, but these economies must be traded off against the diseconomies of distance and adapting site-specific results (the costs of "transporting" the research results to economically "more distant" locations). Thus, as the size of the research enterprise increases, unit costs are likely to decline at first (because economies of size are relatively important) but will eventually rise (as the costs of economic distance become ever-more important).

Given the United States dominates the world totals, its trends are worth scrutinizing. Ranked in terms of total hectarage, the world and US crop relativities for 2002 are the same–soybean dominates, followed by corn and cotton. However, the intensity of use of bioengineered versus classically bred crops differs between the Unites States and the rest of the world. The United States uniformly makes more intensive use of bioengineered crops than the rest of the world (Figure 29.4). Although 77% of the US canola crop was sown to bioengineered varieties in 2002, the corresponding rest-of-world share was 12%. Likewise, bioengineered soybeans covered 71% of the US soybean hectarage and only 28% of the rest-of-world

[15]For example, all the officially approved Monsanto/DeltaPine bioengineered cotton varieties grown in China are the same varieties grown in the United States, while most of the bioengineered Chinese varieties are based on older DeltaPine varieties introduced into China in the 1940s and 1950s (Pray *et al.*, 2002). Likewise the transgenic cotton varieties grown in Mexico are from the United States (Traxler *et al.*, 2003), and in South Africa, NuCotn 37-B, an American variety, is widely used (Thirtle *et al.*, 2003).

[16]A close analogy can be drawn with spatial market models of food processing in which processing costs fall with throughput but input and output transportation costs rise with throughput so that when the two elements of costs are combined a U-shaped average cost function is derived (Sexton, 1990).

soybean area.[17] For cotton the corresponding shares were 71% for the United States and 11% for the rest of the world; for corn it was 34% for the United States and 1.4% elsewhere. This reflects both technology and market realities. Although the dominant bioengineered traits (to date targeting mainly budworm/boll weevil complexes in cotton, European stem borers in corn, and Roundup® and Liberty Link® resistance in soybeans and canola) have yield-enhancing or cost-reducing consequences for rest-of-world farmers, they are especially consequential for US producers. And, given their earlier regulatory approval in the United States, these traits are now incorporated into a myriad of locally optimized crop varieties.

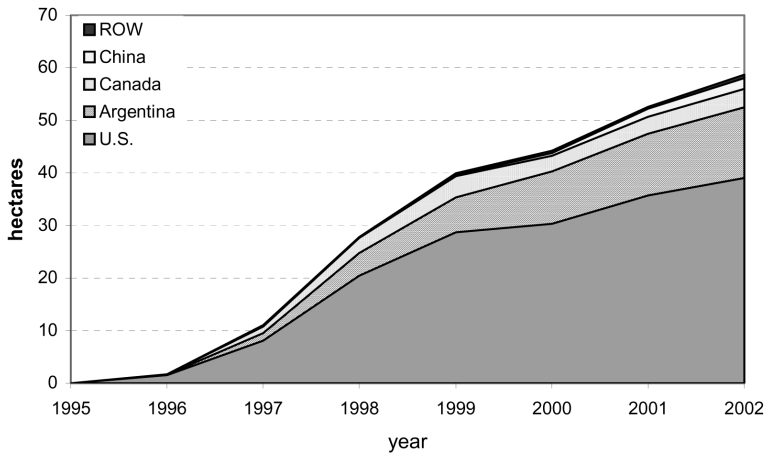


Figure 29.3. Area Sown to Bioengineered Crops Worldwide.
Source: Authors based on data from James (2002 and various years).

[17]In some US states, the share of 2002 soybean acres planted to Roundup Ready® soybeans approached 90% (Marra *et al.*, 2003).

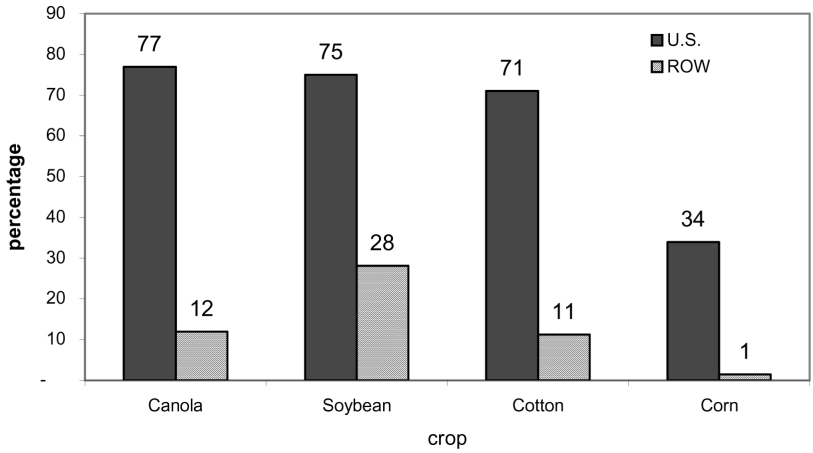


Figure 29.4. Bioengineered Cropping Intensities—United States vs Rest-of-the-World, 2002.
Source: Authors based on data from USDA, NASS (2003) and James (2002).
Note: Data represent share of respective crop acreage in each region sown to bioengineered varieties.

Conclusion

We have shown that the preponderance of research conducted on bioengineered crops is carried out in rich countries (which is where the overwhelmingly large share of biotechnology hectarage is still to be found), and much of the product development work is done by private firms. Moreover, most of the bioengineered traits and the specific crop varieties that are planted in developing countries are spillovers from, or adaptive modifications of, rich-country research. Only when we achieve a reasonable rate of inventor appropriability of the returns to the technologies that are applicable in developing countries, combined with an economic infrastructure that facilitates adoption of those technologies, can we expect a significant private sector role to emerge in the poorer parts of the world.

We also drew attention to the comparatively low rates of investment in public agricultural R&D in developing countries, where government revenues may be comparatively expensive (because it is comparatively expensive to raise government revenues through general taxation measures), or have a comparatively high opportunity cost.[18] Many developing countries are characterized by underinvestment in a host of other public goods, such as transportation and

[18]Alston and Pardey (2003) develop these and related ideas in more detail.

communications infrastructure, schools, hospitals, and the like, as well as agricultural science. These other activities, like agricultural science, might also have high social rates of return.[19]

Even among the rich countries of the world, most have not had very substantial private or public agricultural science industries; so why should we expect the poorest countries of the world to be more like the richest of the rich in this regard?[20] The lion's share of the public (as well as private) investment in agricultural science has been undertaken by a small number of countries, and these have also been the countries that have undertaken the lion's share of scientific research, more generally.[21] An important consideration is economies of size, scale, and scope in research, which influence the optimal size and portfolio of a given research institution. In some cases the "optimal" institution may efficiently provide research for a state or region within a nation, but for some kinds of research the efficient scale of institutions may be too great for an individual nation (Byerlee and Traxler, 2001). Many nations may be too small to achieve an efficient scale in much if any of the relevant elements of their interests' in crop biotechnology research, except perhaps in certain types of adaptive research.

Historically there have been large spillovers of improved varieties (and the technology and know-how embodied in them) among countries. However, as Alston and Pardey (2003) emphasize, we cannot presume that the rich countries of the world will play the same roles as in the past. In particular, countries that in the past relied on technological spillovers from the North may no longer have that luxury available to them in the same ways or to the same extent. This change can be seen as involving three elements:

- The types of technologies being developed in the rich countries may no longer be as readily applicable to developing countries as they were in the past. The agenda in richer countries is shifting away from areas like yield improvement in major crops, to other crop characteristics and even to nonagricultural issues.

[19]As Alston and Pardey (2003) point out, there are also political factors at play here. In rich countries, agriculture is a small share of the economy and any individual citizen bears a negligible burden from financing a comparatively high rate of public investment in agricultural R&D (for instance, in the United States expenditure of US$2 billion on agricultural R&D amounts to less than US$10 per person per year). The factors that account for high rates of general support for agriculture in the industrial countries can also help account for their comparatively high public agricultural research intensities. In many developing countries, where agriculture represents a much greater share of the total economic activity, and where per capita incomes are much lower, a meaningful investment in public agricultural research might have a much more appreciable impact on individual citizens–and the problem is that this burden is felt now, while the payoff it promises may take a long time to come, and will be much less visible when it does.

[20]As noted by Pardey and Beintema (2001), the geographical concentration among countries of particular classes of research–for instance research into agricultural chemicals or machinery–is even greater than that for agricultural R&D in total.

[21]Pardey and Beintema (2001) report that the United States conducted 42% of the world's total investment in all science in 1995.

- The private presence in rich country agricultural R&D has increased, and many biotech companies are not as interested in developing technologies for many developing country applications. Even where they have such technologies available, they are often not interested in pursuing potential markets in developing countries, for a host of reasons.
- Those technologies that are applicable and available are likely to require more substantial local development and adaptation, calling for more sophisticated and extensive forms of scientific R&D than in the past (for instance, more advanced skills in modern biotechnology or conventional breeding may be required to take advantage of enabling technologies or simply to make use of less-finished lines that require additional work to tailor them to local production environments).

In short, different approaches may have to be devised to make it possible for developing countries to achieve equivalent access and to tap into technological potentials generated by rich countries. In many instances, developing countries may have to extend their own R&D efforts farther upstream, to more fundamental areas of the science.

Some argue that strengthening intellectual property regimes in poorer countries is one way of stimulating investments in developing country R&D as well as efforts to commercialize crop technologies developed elsewhere. Others argue that the number and breadth of patents, plant breeders' rights, and other forms of intellectual property is already hindering the R&D required to tackle food security concerns of poor countries. Binenbaum *et al.,* (2003) studied the situation for the 15 staple food crops of the world, and concluded there was undue concern that intellectual property rights were currently limiting the freedom to operate for research on developing country food staples. This paper reinforced the IP evidence they assembled for some key enabling technologies used in agriculture–IPRs concerning crop biotechnologies are overwhelmingly concentrated in rich-country jurisdictions, meaning poor-country research can proceed largely unencumbered by any intellectual property restraints. Binenbaum *et al.,* (2003) also showed that bilateral trade in food staples from poor- to rich-country jurisdictions–where the IP was presumptively in force–was meager (and limited to just a few crops from a few poor countries), meaning the results of this research can be disseminated and used with few if any IP impediments, if the intent is to feed and cloth poor people in poor countries.

As things stand today, the constraints to conducting modern crop biotechnology research in developing countries appear to lie largely beyond IP concerns. Market considerations limit substantial private interests for many crops in many developing countries, and the intensity of public investments is generally low for reasons that do not seem likely to change soon.[22] Intellectual property rights may have a role to play in stimulating efforts to commercialize crops in developing countries, especially

[22]Some even see a scientific apartheid taking shape, with large parts of the developing world being left behind or denied the prospects science has to offer for growth, development, and prosperity (Serageldin, 2001).

helping to harness spillin technologies developed elsewhere, but, at least in the nearer term, they will be no substitute for rich and poor country governments alike reinvesting in the R&D required to maintain and continue adding to the crop yields necessary in the decades ahead.

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References

Adams, J.D. 2001. Comparative Localization of Academic and Industrial Spillovers. NBER Working Paper No 8292. Washington, DC: National Bureau of Economic Research.

Alston, J.M. 2002. Spillovers. Australian Journal of Agricultural and Resource Economics 48(3): 315-346.

Alston, J.M., and P.G. Pardey. 2003 Developing Country Perspectives on Agricultural R&D–New Pressures for Self Reliance?" Chapter 2 in P.G. Pardey, J.M. Alston, and R.R. Piggott. (eds.) Agricultural R&D Policy in the Developing World. Washington D.C.: International Food Policy Research Institute. (In process.)

Alston, J.M., and R.J. Venner. 2002. The Effects of the US Plant Variety Protection Act on Wheat Genetic Improvement. Research Policy 31:527-542.

Alston, J.M., and P.G. Pardey. 1999. The Economics of Agricultural R&D Policy. Chapter 2 in J.M. Alston, P.G. Pardey, and V.H. Smith (eds.) Paying for Agricultural Productivity, Baltimore: Johns Hopkins University Press.

Binenbaum, E., C. Nottenburg, P.G. Pardey, B.D. Wright, and P. Zambrano. 2003. South-North Trade, Intellectual Property Jurisdictions, and Freedom to Operate in Agricultural Research on Staple Crops. Economic Development and Cultural Change 51(2): 309-336.

Byerlee, D. 1996. Modern Varieties, Productivity, and Sustainability: Recent Experience and Emerging Challenges. World Development 24 (4): 697–718.

Byerlee, D., and P. Moya. 1993. Impacts of International Wheat Breeding Research in the Developing World, 1966-90. Mexico City: Centro Internacional de Mejoramiento de Maiz y Trigo (CIMMYT).

Byerlee, D., and G. Traxler. 2001. The Role of Technology Spillovers and Economies of Size in the Efficient Design of Agricultural Research Systems. Chapter 9 in J.M. Alston, P.G. Pardey, and M. J. Taylor (eds.) Agricultural Science Policy: Changing Global Agendas. Baltimore: Johns Hopkins University Press.

Cohen, W. A., R.R. Nelson, and P.P. Walsh. 2000. Protecting their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or not). NBER Working Paper No. 7552, Washington, DC: National Bureau of Economic Research.

Community Plant Variety Office (CPVO). 2002. Annual Report, 2001. Community Plant Variety Office, Paris.

Fan, S., C. Chan-Kang, K. Qian, and K. Krishnaiah. 2003. National and International Agricultural Research and Rural Poverty: The Case of Rice Research in India and China. EPTD Discussion Paper No. 109. Washington, DC: International Food Policy Research Institute.

Fernandez-Cornejo, J., and W.D. McBride. 2002. Adoption of Bioengineered Crops. Agricultural Economic Report No. 810. Washington, DC: Economic Research Service, USDA.

Graff, G.D., G.C. Rausser, and A.A. Small. 2003. Agricultural Biotechnology's Complementary Intellectual Assets. Review of Economics and Statistics, 85(2):349-363.

Graff, G.D., S.E. Cullen, K.J. Bradford, D. Zilberman, and A.B. Bennett. 2003. The Public-Private Structure of Intellectual Property Ownership in Agricultural Biotechnology. Nature Biotechnology, 21(9): 989-995.

Griliches, Z. 1957. Hybrid Corn: An Exploration in the Economics of Technological Change. Econometrica, 25(4): 501-522.

Hall, B.H., and R.H. Ziedonis. 2001 The Patent Paradox Revisited: An Empirical Study of Patenting in the U.S. Semiconductor Industry, 1979-1995. Rand Journal of Economics 32(1): 101-128.

Heisey, P. W., M. Lantican, and H. J. Dubin. 1999. Assessing the Benefits of International Wheat Breeding Research: An Overview of the Global Wheat Impacts Study. Part 2 in P. L. Pingali, ed. CIMMYT 1998-9 World Wheat Facts and Trends: Global Wheat Research in a Changing World: Challenges and Achievements. Mexico City: Centro Internacional de Mejoramiento de Maiz y Trigo (CIMMYT).

Heller, M., and R. Eisenberg. 1998. Can Patents Deter Innovation? The Anticommons in Biomedical Research. Science, 280: 698-701.

Henson-Apollonio, V. 2003. Patent Protection for Plant Material. Paper presented at WIPO-UPOV Symposium on the Co-Existence of Patents and Pant Breeders' Rights in the Promotion of Biotechnology Developments" Geneva, October 25, 2002. Available at http://www.upov.org/en/documents/Symposium2002/pdf/wipo-upov_sym_02_4.pdf.

International Seed Federation (ISF). 2003. Estimated values of the commercial markets for seed and planting material for some countries. Switzerland: International Seed Federation, Available at www.worldseed.org/statistics.html.

Jaffe, A.B. 2000. The U.S. Patent System in Transition: Policy Innovation and the Innovation Process. Research Policy 29(4-5): 531-557.

James, C. 2002. Various years. Global Status of Commercialized Transgenic Crops. Ithaca: International Service for the Acquisition of Agri-Biotech Applications (ISAAA).

Janis, Mark D., and Jay P. Kesan. 2002. U.S. Plant Variety Protection: Sound and Fury…? Houston Law Review, 39(3): 727-778.

Jensen, R., and M. Thursby. 2001. Proofs and Prototypes for Sale: The Licensing of University Inventions. American Economic Review, 91(1):240-259.

Kitch, E.W. 1977. The Nature and Function of the Patent System. Journal of Law and Economics, 20: 265-290.

Knudson, M.K., and C.E. Pray. 1991. Plant Variety Protection, Private Funding, and Public Sector Research Priorities. American Journal of Agricultural Economics, 73: 882-886.

Knudson, M.K., and V.W. Ruttan. 1988. Research and Development of a Biological Innovation: Commercial Hybrid Wheat. Food Research Institute Studies, 21(1): 45-68.

Koo, B., and B. Wright. 2002. Economics of Patenting a Research Tool. EPTD Discussion Paper No.88. Washington D.C.: International Food Policy Research Institute.

Koo, B., P.G. Pardey, K. Qian, and Y. Zhang. 2003 The Economics of Generating and Maintaining Plant Variety Rights in China. EPTD Discussion Paper No. 100. Washington, D.C.: International Food Policy Research Institute.

Lanjouw, J, A., Pakes, and J. Putnam. 1998. How to Count Patents and Value Intellectual Property: The Uses of Patent Renewal and Application Data. Journal of Industrial Economics 46(4): 405-432.

Levin, R., A.K. Klevorick, R.R. Nelson, and S.G. Winter. 1987. Appropriating the Returns from Industrial Research and Development. Brookings Papers on Economic Activity 3:783-820.

Marra, M.C., P.G. Pardey, and J.M. Alston. 2003. The Payoffs to Transgenic Field Crops: An Assessment of the Evidence. AgBioForum online 5(2). available at <http://www.agbioforum.org/v5n2/v5n2a02-marra.htm>.

Mazzoleni, R., and R.R. Nelson. 1998. The Benefits and Costs of Strong Patent Protection: A Contribution to the Current Debate. Research Policy, 27: 275-286.

Merges, R.P., and R.R. Nelson. 1990. On the Complex Economics of Patent Scope. Columbia Law Review, 90: 839-916.

Morris, M.L. 1998. Overview of the World Maize Economy. In M.L. Morris (ed.) Maize Seed Industries in Developing Countries. International Maize and Wheat Improvement Center, Mexico.

Nordhaus, W. 1969. Invention, Growth and Welfare: A Theoretical Treatment of Technological Change. Cambridge Massachusetts: MIT Press.

Olmstead, A.L., and P.W. Rhode. 2002.The Red Queen and the Hard Reds: Productivity Growth in American Wheat, 1800-1940. Journal of Economic History, 62(4): 929-966.

Pardey, P.G., J.M. Alston, C. Chan-Kang, E. Castello Magalhães, and S.A. Vosti. 2004. Assessing and Attributing the Benefits from Varietal Improvement Research in Brazil. IFPRI Research Report No 136. Washington, DC: International Food Policy Research Institute.

Pardey, P.G., and N.M. Beintema. 2001. Slow Magic: Agricultural R&D a Century After Mendel Food Policy Report. Washington, DC: International Food Policy Research Institute.

Pardey, P.G., J.M. Alston, J.E. Christian, and S. Fan. 1996. Hidden Harvest: U.S. Benefits from International Research Aid. Food Policy Report, Washington, DC: International Food Policy Research Institute.

Perrin, R.K., K.A. Kunnings, and L.A. Ihnen. 1983. Some Effects of the US Plant Variety Act of 1970. Economics Research Report No. 46, North Carolina State University, Raleigh, NC.

Pray, C.E., J. Huang, R. Hu, and S. Rozelle. 2002. Five Years of Bt Cotton in China–The Benefits Continue. Plant Journal 31(4): 423-430.

Runge, F.C., B. Senauer, P.G. Pardey, and M.W. Rosegrant. 2003. Ending Hunger in Our Lifetime: Food Security and Globalization. Baltimore: John Hopkins University Press.

Schankerman, M. 1998. How Valuable Is Patent Protection? Estimates by Technology Field. RAND Journal of Economics, 29(1): 77-107.

Serageldin, I. 2001. Changing Agendas for Agricultural Research. chapter 2 in J.M. Alston, P.G. Pardey, and M. J. Taylor. (eds.) Agricultural Science Policy: Changing Global Agendas. Baltimore: Johns Hopkins University Press.

Sexton, R.J. 1990. Imperfect Competition in Agricultural Markets and the Role of Cooperatives: A Spatial Analysis. American Journal of Agricultural Economics 72: 709-720.

Thirtle, C., L. Beyers, Y. Ismael, and J. Piesse. 2003. Can GM-Technologies Help the Poor? The Impact of Bt Cotton in Makhathini Flats, KwaZulu-Natal. World Development, 31(4):717-732.

Traxler, G., S. Godoy-Avila, J. Falck-Zepeda, and J. Espinoza-Arellano. 2003. Transgenic Cotton in Mexico: Economic and Environmental Impacts. Chapter in N. Kalaitzandonakes (ed.) Economic and Environmental Impacts of First Generation Biotechnologies, Kluwer Academic: New York.

UPOV. 2003a. Plant Variety Protection Statistics for the Period 1998 - 2002. C/37/7, Geneva: International Union for the Protection of New Varieties of Plants.

UPOV. 2003b. Plant Variety Database CD 2003/02. Geneva: International Union for the Protection of Plant Varieties.

USDA, National Agricultural Statistical Service (NASS). 2003. Acreage Reports" downloaded from http://usda.mannlib.cornell.edu/reports/nassr/field/pcp-bba. Washington, DC: U.S. Department of Agriculture, National Agricultural Statistical Service.

World Bank. 2004. World Development Indicators Database 2004. Washington, DC: World Bank.

Chapter 30

IPRs: Must There be a Conflict Between Commercial Need and Humanitarian Benefits?

Anatole Krattiger and Malcolm Elliott

Introduction

A fifth of the world's population lives in abject poverty (income under US$1 per day) and almost half in poverty (income under US$2 per day). Poor people in indebted countries have inadequate access to food and lack a healthy diet (UNDP, 2004). They spend up to 80% of their low incomes on food, and this usually translates into acute food insecurity. Moreover, their diets are often deficient in vitamins and minerals, leading to malnutrition and disease.

There are technologies that could alleviate the plight of the poor, but poverty reduction and economic development always need a stable base of agricultural production, especially because most people in developing countries depend on agriculture for their livelihood. In this regard, science-based agricultural improvements play an important role. For example, recent developments and new breakthroughs in molecular and cell biology (often included under the title "biotechnology") provide new and more sophisticated tools for the genetic enhancement of crops, fish, and livestock, thereby improving yield potential as well as the nutritional value of food—even under stress or in marginal environments. To exploit these advances we need efficient and inclusive partnerships that respond coherently to the needs of the poor, especially in rural areas.

Vitamin A deficiency (VAD) is one such problem. In many areas of the world where rice is a basic staple food, thousands of poor people lose their eyesight because of VAD. In fact, severe VAD (xerophthalmia, also called night blindness) leads to permanent blindness, with 500,000 people, of whom 250,000 are children, going blind every year (WHO, 2000). VAD leads to a depressed immune system that increases the incidence and severity of infectious diseases and infant mortality rates. In fact, the mortality of these children is nine times higher than that of normal children. Inevitably, the children most at risk of infectious diseases due to poverty

and inadequate sanitary conditions are also the ones most prone to VAD. It is a vicious circle. The more children suffer from anaemia, diarrhoea, and other ailments, the less vitamin A they absorb.

Most, if not all, of these infant deaths are preventable. In adults, the implications can also be serious, particularly for pregnant and lactating women. Over half a million women die each year from childbirth-related causes, many of them from complications that could have been reduced or prevented entirely with better provision of vitamin A. Again, it is the mothers of the poorer segment of the population that are most affected because their lack of purchasing power leads to an inadequate diet, poor in vegetables, fruit and other sources of Vitamin A. "Golden Rice" is a powerful example of the way such problems could be addressed. This rice is genetically enhanced to produce pro-vitamin A, which gives the rice grains a light golden color. Golden Rice could deliver vitamin A in the rice grains eaten by needy people (Potrykus, 2000).

Biotechnology, IPRs, and Public Good

Major scientific advances in plant breeding delivered the Green Revolution, which was the most important contribution to world food security during the last century. It resulted in significant increases in production and productivity, primarily in staple cereal crops such as wheat, rice, and maize. Per capita production increased 33% over the last 50 years from 275 to 370 kg per person per year. That rate of increase is, however, beginning to plateau, and new technologies are needed to maintain the increases required to deliver food security for everyone. In this context, the major development that spurred private sector investments in agriculture was the patenting, in the USA in 1980, of a living organism in the landmark case of Diamond vs. Chakrabarty, in which the United States Supreme Court ruled that patents could be granted for "anything under the sun that is made by the hand of man." That includes living organisms. Since the tools and products of biotechnology could thenceforth be protected from appropriation for a limited period of time (typically 20 years from the date of filing the patent), significant private resources have been flowing into this new technology. Major established businesses, especially those in the chemical industry, espoused biotechnology because the industry saw in it a sustainable long-term future.

In most legislation worldwide it is considered reasonable for an inventor to be given a monopoly, or the right to exclude others from the sale or use of the invention for a limited time, in return for a full public disclosure of how the invention is performed. In economic terms this right of exclusivity is important for the inventor to be able to recover the investment in the research, while not giving the competitor(s) free access to the newly created knowledge That said, the public disclosure of the invention allows competitors to improve upon, or to work around, the patent.

It is well proven that a framework of intellectual property rights (IPR) protection, with its right to limited exclusivity, has served to foster research and development. Biotechnology is often used as an example and it is particularly relevant today. The boom in investment in biotechnology and information science continued throughout the 1990s and into the 21st century. The US Patent and Trademark Office (USPTO, www.uspto.gov) has more patents pending than it has issued in its entire 200-plus year history, most of them in biotechnology and information technology. This serves as an indirect indicator of the stimulus intellectual property protection has provided to research investment.

Dealing with IPR issues has been a slow process for national and international agricultural R&D institutions. Essentially, companies are built around IPRs, whether they be trademarks (such as Starbucks coffee), or trade secrets (such as Coca Cola), or key patents (such as those of DuPont and many others). The public sector, however, for a very long time felt that it did not deal with IPRs since it was serving the public good. The public good, however, does not need to be invented, developed, or produced by the public sector in order to be a public good. Many public goods are supplied by the private sector, such as street lamps or traffic signals. This misconception has led to much delay in the judicious use of IPRs to benefit the public good and in improving the efficiency with which private (bio)technologies reach small-scale and resource-poor farmers. A number of factors responsible for this are discussed below.

IPRs, Territoriality, Licensing, and Risk

IPRs are territorial rights; that is, national institutions issue such rights that allow the owners to prevent others from using an invention. The patents issued by the USPTO, for example, are only valid in the USA and nowhere else. Inventors, however, have the option also to file for patent protection in many other jurisdictions (countries), provided their inventions are patentable in those countries. Hence, only the USA and a few other countries issue utility patents on plants. Each additional filing, however, brings with it significant additional costs. Thus an inventor has to make important decisions as to where to file, how long to maintain a patent, and what licensing strategy to adopt. Many companies file in jurisdictions where they have no current business activities. They hope to identify a potential licensee to license their inventions for a share in the value added, which is recouped through royalty rates.

Preventing third parties from using a certain patented invention is only economically appropriate if the owner of the invention wants to exploit it in a particular market. In the absence of any direct economic or strategic interests, it is economically unsound to prevent others from using an invention. A patent, therefore, is either exploited directly by the owner of the invention (technically the assignee), or through licensing. It should be noted that such licensing can take many different forms, such as exclusive or nonexclusive, or as part of a cross-licensing deal.

If a particular invention is not filed or issued in a given country, then anyone is totally free to use the invention in the countries where no patents are issued. As soon as a product containing a patented invention is imported to a country where the patent is issued, then a license would be required. At this stage, the owner of the invention has a choice: agree or not agree to a license. In the first case, the license may be royalty-bearing or royalty-free. In the second case, even if no license is granted, it does not necessarily mean that the product can no longer be imported. In fact, in many cases patent holders either do not know that a product contains their invention, or deem it economically inappropriate to enter into time-consuming, and thus costly, licensing negotiations.

From a strategic point of view, the exporter will need to conduct a freedom-to-operate (FTO) review to determine what patented inventions are contained in a given product, and in which territories, or jurisdictions, they apply. Such FTOs, however, bear a significant level of uncertainty and risk.

Typically, identified patents fall into three groups: patents that are definitely applicable; patents that may or may not apply depending on how one interprets the claims and argues the case; and patents that may be related to the product but not really covering the product. It is the second group that presents a considerable level of risk.

Let us assume there are 15 patents in the second group, which are owned by a total of six entities (public or private). It would mean that six licenses need to be obtained just to be on the safe side. That involves cost and time. Alternatively, the exporter may decide that the level of risk is relatively low and not pursue a license. In this case, there are four possible outcomes.

- There may never be a problem.
- One of the patent owners may approach the importer and this may lead to a license.
- A patent owner approaches the importer, but the importer argues that their products are not covered by the patent and thus do not infringe the patent. In many cases, such disputes end there. Only if a lot of money is potentially at stake would such a dispute be taken to court. And if it does go to court, most disputes are settled out of court (a license is agreed upon commensurate with the value added through the invention).
- Only in a very few cases would the fourth outcome occur: the importer is blocked from importing the product.

One of the problems with the public sector, especially in national and international agricultural research, is that the few cases that fall within the terms of the fourth outcomeabove (in the authors' estimate perhaps less than 1%) receive all the publicity. Further, they are risk-averse when it comes to IPRs and licensing. It is almost impossible to resolve all IPR issues around a single product, and one will always need to assume some level of risk if one goes to the market, whether for commercial production or for subsistence agriculture. Effective IPR management is, from many perspectives, nothing but risk management. It allows an organization's

managers to address questions related to the level of risk that their organization is willing to accept in regard to the organization's financial support, its reputation, and its overall effectiveness as an organization. Because IPR management is risk management, and because one does not always know beyond a reasonable doubt who owns which rights concerning particular IPR claims, active management of an organization's IPR portfolio is essential for an organization's continued existence.

Material Transfer Connection

Until the mid to late 1990s, many international agricultural research centers would obtain biotechnologies under material transfer agreements (MTAs) that would allow them to conduct research. Most of this work, however, especially in breeding, is actually product development (and thus would require a commercial license, royalty-bearing or royalty- free). Only late in the product development stage did it become clear that in order for any new materials to be transferred to third parties, whether they were other public research and breeding entities or farmers, new agreements would need to be negotiated. Had the same technologies not been obtained through MTAs, but developed independently, then no license would have been needed since, in most of the developing world, many of the biotechnology research tools or products (for example, genes) are not patented nor, in many cases, patentable. The technology owners, having agreed to terms under MTAs, were essentially provided with an extension into territories where no rights were previously enforceable. MTAs are contracts that are almost universally enforceable to a greater or lesser degree.

In the absence of an MTA, or any other type of technology transfer agreement, no licenses are required to use a given technology in countries where the given inventions are not patented. This is not unusual; any company would do the same. In other words, if a multinational company or small start-up company did not require a license (either for legal reasons or for practical reasons[1]), then no license will be agreed upon. Again, there may be exceptions to this generalization that relate to strategic interests but these are the exception rather than the rule.

For the public sector in international agricultural R&D, this more "businesslike" attitude has rarely, if ever, been adopted. Some argue that it would damage relationships, whereas others argue that the financial donors to these institutions, based in the countries where the corporations are headquartered, would view such "infringements" as negative and thus funding would dry up. First of all, the act of using a patented invention in countries where the invention is not protected does not constitute an infringement. Second, these are the rules of the "game" which corporations also adopt. And third, the best long-term strategy for any corporation to

[1]Practical reasons mainly refer to the licensing of know-how and/or trade secrets. In some cases, such as in fermentation, it is often advantageous to in-license know-how/trade secrets due to the time and cost saving nature of such technology transfers.

license its technology is to have strong entities in place that can "absorb" their technologies (that is, which have a certain level of technological capacity). It is rarely the first few products that come out that will lead to major financial rewards.

What is of much greater importance is to establish product quality and product stewardship. This is a far bigger constraint in biotechnology transfer in both humanitarian and commercial transfers. In fact, the authors argue that if a company has ownership rights to a certain product or technology, then it only makes that entity more interested in collaboratingto ensure that the fruits of its inventive endeavors are reaped in both humanitarian and commercial terms.

Hence international R&D institutions should be in a strong position to obtain licenses even if MTAs had previously been signed, provided product stewardship has been addressed. This means dealing authoritatively with biosafety, field trials, and quality control all the way down to the production and distribution plans for the improved seeds.

Market Segmentation and Future IPR

IPRs per se do not conflict with commercial or humanitarian uses, provided they are properly managed (Byerlee and Fischer, 2001; Lybbert, 2002). Proprietary technology, evidently, can serve both needs provided the markets are properly segmented into commercial, semicommercial, or noncommercial/humanitarian. Two fundamental aspects need to be addressed to make this possible: one is authoritative IPR management and the other is product/technology stewardship.

We are not stating, however, that managing that interface, or nexus of the commercial and humanitarian aspects, is going to be easy or free of charge. Modest investments in authoritative IP management, however, will make existing investments more effective. Sound institutional strategies and policies are required to build on the comparative advantage of the public entity and manage the "market segmentation" that must underpin the dual use of protected technologies. Until now, the public sector in international agricultural R&D has, overall, been significantly underfunded in IPR management, with a typical center with a budget of some US$20 million maybe having one IPR management officer on its staff, and with little use of outside or General Counsel. The functions of a General Counsel should be to provide services in three broad areas:

- General and consistent advice on the institution's contractual agreements.
- Proactive advice regarding the legal aspects of the institutional plans and business strategies.
- Leadership for legal responses, in the event that the institution is faced with overt legal actions.

Similarly, the public sector must be more willing to take risks, based on sound inputs and information, such as those of General Counsel. This will require a shift in the manner in which the public sector thinks and operates. We are not promulgating the view that the public sector should play by the same rules as a corporate entity to aggressively defend its strategic interests. However, the public sector should be prepared to take normal risks that come with typical IPRs and obligations, be they generated through in-house inventions or by third parties.

IPRs and Other Areas

IPR management is a tool that can be used to assist in the effective deployment of new technologies. There are, however, a number of places where IPRs closely interface with other frameworks. Because of this close interface, it is not uncommon to find a mixed agenda on a number of topics. This agenda mixing, while complex, is important as it fits into the jigsaw puzzle of product development and deployment.

Regulatory matters

In most cases, the production and sale of a particular advanced research product will require some form of government clearance. This clearance will often relate to the health and safety issues of the product. It follows therefore that the ownership rights and regulating obligations of a particular advanced research product may have an impact on such approvals. Likewise, ownership of an advanced research product's IPR will impact the liability issues that may arise from the sale of such products.

Biosafety

Again, there are often concerns over the freedom to test materials (for example, transgenics) based on a perceived or actual risk of biological hazards. In some circumstances a product may be safe to deploy, but ownership rights issues prevent such testing/deployment. In other cases, the ownership of IPRs may be clear but the material has not received biosafety approval for testing.

Liability issues

Product liability issues probably deserve an entire section to themselves, and they will usually form a part of a formal freedom to operate opinion letter. Liability may surface in a number of ways. It may be directly related to IPR ownership matters,

such as patent or copyright infringement or the violation of contract rights. It may be related to warranties that a product will perform in a certain manner (expressed in an MTA or contract agreement). There can, of course, be direct product tort liabilities related to the production or use of the product. Again, care is needed since many of these aspects of liability may be dealt with in contractual agreements associated with the transfer of the technology ownership rights.

Treaties and conventions

A number of different treaties and conventions impact the area of IP rights. These treaties may be derived from the science, such as the Convention on Biological Diversity, or they may be derived from the law, such as the Patent Cooperation Treaty. These forms of "International Law" are then enacted, often in modified form into each country's legislation. This jurisdictional aspect of IPR management law is crucial when analyzing liability issues and the scope of protection under a freedom to operate review (Kryder et al., 2000).

Conclusions

Several broader questions are warranted; the answers to these, or rather the strategies that are being developed in response to them, will to a large extent determine whether or not, or to what extent, IPRs contribute to both commercial and humanitarian goals.

One of the key issues is whether agricultural research is in some way really "special" as it relates to IPRs and IPR management. The fact that human well-being depends on food, the time frames involved with the research process, and the underpinning of free global access to genetic resources, all feed into this special status concept. Some of the critical questions in this area that must be addressed by policymakers at the international, national, and institutional levels are asked below. We also offer our own answers to these questions (Dodds and Krattiger, 2003):

- Does IP protection stimulate research investment in agriculture?
  We believe the answer is clearly yes. Since the ruling of the Supreme Court in the USA that allowed for the patent protection of living organisms (mentioned above), there has been a massive investment in life sciences research. Many of the advances being used by the international agricultural research community, including genomics, would not have been possible without the billions of US dollars invested by the private sector over the past twenty years. The more fundamental question is:
- Can proprietary research contribute to developing country research?
  Our answer to this is definitely yes. There is no reason to believe that innovative

research is less valuable as a matter of geography. The growth of the software development industry in India and other parts of Asia, and now in parts of Eastern Europe and the newly independent states, serves as an example of this. Several multinational seed companies are already investing heavily in new research infrastructure in developing countries. More can and should be done. Another example is the new Biosciences Eastern and Central Africa being established on the International Livestock Research Institute campus in Nairobi, Kenya. Clearly, the idea here is to harness the research already accomplished for the benefit of developing country advances in research.

- Should governments or institutions see this as a revenue source or only cost recovery?

  The minimum here is cost recovery, but as with not-for-profit research foundations in the industrial countries, why not allow any "profit" to be reinvested into these organizations to further the development of more research output? In Egypt, the Agricultural Genetic Engineering Research Institute (AGERI) has set up a foundation to allow the benefits of its license agreements with Pioneer Hi-Bred International to funnel back into more research. Many universities in the USA, especially since the Bayh-Dole Act of 1980, are practicing this without much fanfare. Although the efficiency and efficacy of the act under today's conditions could be discussed at length, overall there have been no major problems in segmenting public research outputs into public and private. Hence the next question is almost a rhetorical one.
- Is there a role for truly "public" goods, both nationally and internationally?

  We believe there is such a role. Producing animals and plants with resistance to certain pests and diseases that do not respect national boundaries is a regional or international public good. Enhanced nutrition to alleviate human diseases associated with poverty is an international public good, and breeding for resistance to climate variation is an international public good. It should be noted here that a public good does not necessarily need to be generated by the public sector. In fact, in many other areas, public goods are generated by the private sector and through public funds made available to society as a public good. New mechanisms must be found in agriculture to involve the private sector more strongly in the generation of public goods, which would benefit the public and the private sector.
- Does publishing play a key role in the public domain?

  Clearly the answer is yes. Should an organization choose to follow a philosophy where it wishes all its research output to be public good in nature … then it must publish the outcomes. Published research is so-called prior art and will serve to bar others from claiming such inventions.

The last question, however, opens an entirely new debate about the public good. The bulk of scientific "knowledge" is in the public domain and forms a body of international public goods. This science, or knowledge, may become private at the level of technologies that work in the marketplace. In agriculture, up until the past

decade most information and materials was so-called public domain material. The Green Revolution was based in large part on materials and knowledge flowing from universities and governmental research and breeding programs. Before the 1980 Bayh-Dole Act all such information was in the public domain. This "privatization" of public sector research has blurred the line in terms of those international bodies that are accessing research materials. As a result, it is no different in essence to negotiate a license agreement with a major university than with a multinational company.

Whether or not the current privatization of public goods is healthy is a very different question. One could argue that it is healthy, as long as the private ownership is balanced with broad research exemptions. In relation to genomics, the questions go further and one should differentiate whether one is talking about the availability of information or the availability of ownership. These are different but related matters. To the scientist the important issue is access to the information. For product development, ownership is critical. In those crops where market forces are not directly applicable, other more innovative license agreements or waivers will be needed.

Further, whether the privatization of these systems is economical is also a much more difficult question to answer. In simple terms, if it is not economical then it will fail under privatization. The question then is whether the government still attaches sufficient strategic priority that it wishes to keep funding it from internal revenues.

Intellectual property rights were developed to define ownership of intellectual and human creations, principally dealing with intangible creations. In debates surrounding IPRs, a major problem stems from the fact that to become useful, such intellectual creations need to be expressed in tangible materials. Although materials in themselves are typically not protected, the value-added human creations are. This poses a significant conceptual problem that we have attempted to clarify.

IPRs are also territorial; that is, national institutions issue them, which allows the owners to prevent others from using an invention. Limiting such access, however, is only economically significant if the owner intends to exploit the invention in particular markets. In the absence of direct economic interests or strategic imperatives, it is economically uninteresting to prevent others from using an invention. However, as IPRs are typically expressed in tangible expressions, two significant problems arise.

First, most inventions are only protected in rich economies. They can therefore freely be used in other countries with a license needed only if products expressing the invention are exported to rich countries. From a humanitarian and development perspective, this should not be a significant stumbling block because if products are exported, it probably means that significant value has been added. In such cases, licensing negotiations on reasonable royalty rates should normally be successful unless such exports directly compete with the holder of the IPR.

Second, the manner in which such tangible expressions are obtained is critical. Typically, scientists collaborate by sharing materials under legally binding agreements. If a product has been developed that used such received material, then a license will have to be obtained for use, whether the invention is protected in that particular country or not.

In both cases, product quality (stewardship) and indemnity (liability) are among the key stumbling blocks to obtaining licenses for both humanitarian and commercial uses. Arguably, the fact that some entity has rights to certain products would only make that entity more interested in collaborating to see the fruits of its inventive endeavors reaped in both humanitarian and commercial terms.

We conclude that IPRs are not obstacles to reaching humanitarian goals, but can be an effective means to engage owners of inventions in humanitarian programs, provided other systemic constraints are addressed successfully.

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References

Byerlee, D., and K. Fischer. 2001. Accessing Modern Science: Policy and Institutional Options for Agricultural Biotechnology in Developing Countries. IP Strategy Today No. 1-2001. www.bioDevelopments.org/ip Last Accessed 15 August 2004.

Dodds, J., and A.F. Krattiger. 2003. Intellectual Property Rights and their Impact on Agriculture in International Development: Key Issues, Future Trends and Options. In: Management of IP in Plant Science in the 21st Century. CropLife International: Bruxelles. pp. 1-21.

Kryder, R.D., S. Kowalski, and A.F. Krattiger. 2000. The intellectual and technical property components of pro-Vitamin A rice (GoldenRice™): A Preliminary Freedom-to-Operate Review. ISAAA Briefs 20. pp. 74.

Lybbert, T.J. 2002. Technology Transfer for Humanitarian Use: Economic Issues and Market Segmentation Approaches. IP Strategy Today No. 5-2002. Pp. 17-25. www.bioDevelopments.org/ip Last Accessed 15 August 2004.

Potrykus, I. 2000. The Golden Rice Tale. AgBioWorld 23 October. http://www.agbioworld.org/biotech_info/topics/goldenrice/tale.html Last Accessed: 15 August 2004.

UNDP. 2004. Human Development Report. http://hdr.undp.org/reports/global/2004/pdf/hdr04_complete.pdf Last accessed: 15 August 2004.

WHO. 2000. Global Initiative for the Elimination of Avoidable Blindness. Fact Sheet 213. WHO: Geneva.

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Chapter 31

Patents, Pharmaceuticals, and Health in Developing Countries

Børge Diderichsen

Introduction

All 191 members of the United Nations have pledged to meet the so-called UN Development Millennium goals by 2015. Two of these goals are:

- In cooperation with pharmaceutical companies, provide access to affordable essential drugs in developing countries.
- In cooperation with the private sector, make available the benefits of new technologies–especially information and communications technologies.

In this context it is important to consider the role of patents and, in particular, to address the question: Do patents increase or inhibit access and development of new technologies in developing countries?

Patents

A patent is a property right granted by a sovereign state to the inventor of a novel, non-obvious and useful invention. Thus, a patent is not a right to produce or to sell, but a right to prevent others from making commercial use of an invention until the patent has expired.

The research-based pharmaceutical industry is one of three technology-intensive industries in which the patent virtually equals the original, nongeneric product. The others are the chemical industry and the biotechnology industry. The reason for this is that the material production cost of a pharmaceutical product usually is low compared to its price, because the largest part of the value of the product is immaterial (intangible), that is, related to knowledge and skills concerning the discovery, development, and approval process. Thus, a new safe and innovative drug represents a highly advanced product of the knowledge and high-tech industry, that on the average costs US$800 million to develop to market.

The immaterial value of drugs is the main reason that the global market for pharmaceutical products was a staggering US$400 billion in 2002. Currently, the USA, EU, and Japan combined account for 80% of this market. A strong patent system is a condition for the protection of this immaterial or intangible value, as well as a motivation to embark on such expensive product development processes. Thus, the US patent protection system–and a market without price controls–is believed to be one of the main reasons for the massive flow of investment into the USA causing expenditures on research to increase from US$1.7 billion in 1977 to US$26.4 billion in 2002 (Lehman, 2003).

Global Divide of Patents and Licenses

OECD (Organisation for Economic Co-operation and Development) estimates that in 1998 its members accounted for 86% of patent applications filed, and 85% of scientific and technical journal articles published worldwide, earning 97% of worldwide royalties and license fees. Developing countries earned 0.05% in the same year. Similar figures have been estimated by UNIDO (United Nations Industrial Development Organization) (Figure 31.1).

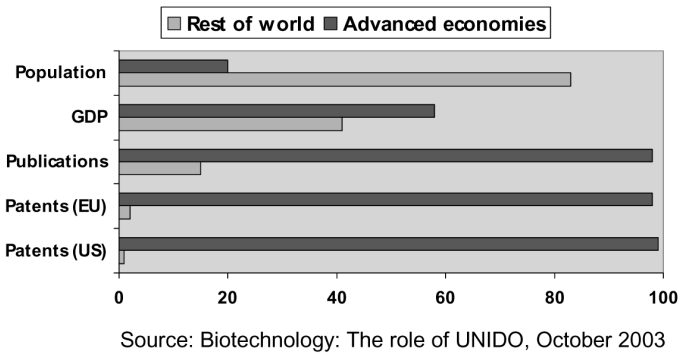


Figure 31.1. The global divide in science and patents.

During 1999-2001, developing countries accounted for less than 2% of US patent applications, with 95% of those originating from China, India, South Africa, Brazil, and Mexico (US Technology Assessment Report, 2002). When it comes to absolute numbers of international patent applications (according to WIPO Annual Report 2002, (www.wipo.int/pct/en)), the USA is leading with 44,609 applications in 2002, while China (1124 applications) and India (480) submitted fewer applications than Finland (1762) and Denmark (989), countries with only 5 million inhabitants. Three applications were recorded from Algeria and none from Egypt in

2002. In summary, there is a major global divide in generation and control of intellectual property rights.

On the other hand, international patent filings have been rapidly increasing over the last year in some developing countries (52% and 20% from Indian and Mexican entities). It therefore appears that some countries are on their way to closing this divide, as several countries in East and Southeast Asia have been able to do successfully since the end of the Second World War.

Patents, Drugs, and Developing Countries

During 1975-99, 1393 new drugs were approved (Ismail Serageldin, Library of Alexandria 2003, citing Troullier et al., The Lancet, 359:2188, 2002). Of these only 13 were for tropical diseases, and only a few of these for tuberculosis, despite the fact that one person is infected by tuberculosis every second, 2 billion people are currently infected, and 2 million people died in 2000 (Pierre Crooy, GlaxoSmithKline Biologicals, 2002, citing WHO, NIAID, and NIH).

This raises the question of why some poor countries are not developing drugs to prevent or treat local diseases. One of several reasons may be that while some developing countries have government-run laboratories active in medical research, the patent incentive is not available to many inventors because there is no effective patent protection for health-related technologies, or qualified support when it comes to technology transfer.

Some of the more advanced developing countries have the capacity to build research-intensive pharmaceutical industries, capable of operating profitably by providing products directed to the diseases common to their own nationals, and supported by the economics of the local market. For such local industries to take root and grow, effective patent protection must be made available. The huge development costs of a new drug cannot be covered without that period of monopoly that patent protection provides.

Until the TRIPs (Trade Related Aspects of Intellectual Property Rights) Agreement in 1994, many developing countries did not provide patent protection for pharmaceutical products. WTO (World Trade Organization) countries have obligated themselves to provide such protection. As a consequence countries such as India, with a considerable and well-known capacity for producing generic drugs (not protected by patents) as well as for research, will most likely develop their own original and patented drugs, some of which will be aimed at local diseases. The recent significant increase in Indian patent applications supports this prediction. It can therefore be expected that in those developing countries that have made best use of the new opportunities and invested cleverly in education, science, and technology, a local, research-based pharmaceutical industry will be established. Society will benefit because of the jobs and the wealth created, and because new preventatives and treatments of some local diseases will be developed.

As for the direct effects of current drug patents on society and patients in developing countries, it should be noted that of the 308 drugs listed by WHO as essential to public health in developing countries, only 5% were patented in any jurisdiction (Lehman, 2003).

Furthermore, TRIPs article 31 permits WTO member states to limit the exclusive rights of patent owners where a national government needs to use the patent itself, or where it is necessary to issue a compulsory license to a third party, such as in a health emergency.

It should also be noted that Oxfam estimates that if Africa could get only a 1% additional share of world trade, that would inject US$70 billion into African economies. If only 10% of that were to go to health, Africa would have the means to confront its health crisis. Seen in this perspective, fighting poverty, not patents, is the way forward.

Conclusion

The UN Millennium Goals are as ambitious as they are justified by our sense of global responsibilities. To achieve them, all stakeholders must participate, including governments, research institutions, pharmaceutical companies, patient organizations, other NGOs (nongovernmental organizations), and international organizations.

Some of the key issues for developing countries are investments in education, science, and innovation. Proper patent protection is a necessary means to reap the benefits of such investments. Patents are a powerful tool for economic growth (Idris, 2003). Japan and Korea are examples that prove the point. China and India are on their way.

What can pharmaceutical companies do? At Novo Nordisk we believe that partnership is essential to cooperate with local partners on how to prevent and treat diabetes, our field of expertise. In India, China, and many other countries, we have extensive collaborations with local health authorities. We have donated US$90 million to the World Diabetes Foundation (www.worlddiabetesfoundation.org), and established research and manufacturing facilities in China and Brazil. This will help build the local competencies that are needed to discover and develop new pharmaceutical products, as well as protecting the intellectual property rights generated locally. This could and should be one of the bases for future trade and technology transfer in biotechnology and pharmaceutical disciplines between developing and industrial countries, to help close the global divide in science and patents.

For our global responsibilities as a pharmaceutical company, the very nature of the role that we can and should play is anything but clear. How far does our social responsibility go? What is the role for governments, WHO, UN, ministries of health and NGOs? The dilemma is clear, the answer is not. But the way forward must be dialogue and partnerships (Lise Kingo, Executive Vice President, Novo Nordisk, 2003, pers. comm.).

References

Lehman, Bruce. 2003. President, International Intellectual Property Institute. www.iipi.org

Idris, Kamil. 2003. Intellectual Property. A Power Tool for Economic Growth. World Intellectural Property Organization.

Chapter 32

Intellectual Property Rights and the Controversy Between Industrial and Developing Countries Over Animal Rights and the Needs of People

Carlos María Romeo-Casabona

Introduction

The original purpose of the European rules concerning biopatents was two-fold: to harmonize the European legislation on biotechnological patents, and to contribute to the development of biotechnological research in Europe. This would help ensure that Europe did not lag behind the North American and Japanese biotechnological market (Lema Devesa, 1999). During the 1990s Europe was involved in an intensive debate, arguing that patenting life should be in compliance with recognized standard ethical principles.

The necessity for a Directive was urgent, because the practice of biotechnological inventions had shown the differences between national laws regarding patents in the different member states. Furthermore, the differences might increase through administrative performance or by juridical interpretation. This could hinder the operation of the market and even reduce the industrial development of inventions in this field.

The current Directive is full of ethical considerations, in the sense that it states a position devoted to solving the ethical questions related to the patentability of living matter, and of parts of the human body, including human genes (Bergel, 2000).

Governments of some countries of Asia (India), Africa (South Africa), and Latin America (Brazil), among others, were confronted with the problem of providing vital drugs (for example, medicines for HIV/AIDS) for their people. It was both an economic concern, as these countries are not complex drug inventors, and an ethical dilemma. because those governments could not just accept the death of thousands of infected persons. There is also a complication, because these countries provide human subjects for some clinical trials (for example, HIV/AIDS drugs) funded by important northern companies. There is a need to ensure that these patients

benefit from the new drugs after the trials are completed (European Group on Ethics in Science and New Technologies to the European Commission, 2003), and to prevent exploitation of the vulnerable (Nuffield Council on Bioethics, 2002).

Patents to Protect Biotechnological Innovations

The important European Directive on the legal protection of the biotechnological inventions (Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998) will have to be considered by Member States, bringing into force laws, regulations, and administrative provisions necessary to comply with the Directive. This has already happened in many states. The European Convention on the Patent of 1973 was revised in 1999 to adapt it to the new legal framework in the Directive.

The new European regulation provides a general response to the numerous concerns that this matter provokes: that the biotechnologies will be legally protected, in a primary or exclusive way, through the patent. Solutions other than the patent have been rejected, setting down the relevant aspects that differentiate a discovery from an invention. This was one of the most controversial points in the favorable or contrary arguments to the patent.

In the Preamble it is proclaimed that it is not sought to substitute the existing national general frameworks on patents, but rather "the rules of national patent law remain the essential basis for the legal protection of biotechnological inventions" (No. 8). There has been considerable interest in emphasizing that it should be demonstrated that the presumed novelty or biotechnological innovation fulfils each and every one of the traditional requirements of the patent. And, concretely, the Preamble and the articles of the Directive stress that the applicant must demonstrate convincingly the industrial application of the biotechnological product. Its utility should be fully defined and clearly exposed as well, although the Directive makes more flexible the understanding of the other two requirements of the patent (to be new and not obvious inventions) when it deals with biotechnology.

Another goal of the authors of the Directive (the Parliament and the Council) is to make as clear as possible what is patentable, particularly in connection with human biological material, or when the human body is somehow involved, but also with animals and vegetables. The Preamble of the Directive seeks to clarify what is intended to be regulated.

What is the new European normative framework that the Directive on the protection of biotechnological inventions establishes? It explicitly appeals to the national law on patents, notwithstanding the necessary adaptations to take account of the provisions of this Directive (article 1). Consequently, according to this prescription, the adequate legal framework for the protection of the biotechnological inventions is the law of patents.

The Directive states, as a general principle, that a product consisting of or containing biological material is patentable. It also states that the process by means

of which biological material is produced, processed, or used is patentable, providing they comply with the traditional requirements of patents. They must be new inventions that involve an inventive step and that are susceptible to industrial application (article 3.1).

Consequently, biological material that is isolated from its natural environment is patentable, and also if it is produced by means of a technical procedure, even if it previously occurs in nature (article 3. 2).

The approach of this Directive regarding the patentability of human genes or parts of them, is based on this precept, because such a possibility is admitted under the above conditions. This does not prevent the Directive from clarifying it even more specifically, as we will confirm next.

Framework on Elements of the Human Body

Regarding human biological material, the Directive points out that such material will be considered as patentable invention. It states: "An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element" (article 5.2). In any case, it emphasizes that "the industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application" (article 5.3).

On the contrary, "the human body, at its various stages of formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions"(article 5.1).

As for the exposed patentability conditions, there is still a debate on whether the sequence of a gene or part of it, isolated in a laboratory or obtained by other technical process, really constitutes an inventive activity. Indeed, it is pointed out that a gene or a functional fraction of DNA can be identified with a chemical molecule. But an essential difference remains: what really is relevant to that molecule is the genetic information it contains, and not its basis itself. If the structure of this information "is identical to the one of a natural element, we have a discovery, not an invention" (Bergel, 2000). Consequently, against the approach of the Directive, according to the contrary opinion, the reproduction by means of a technical procedure or the isolation of that information or knowledge would not constitute an inventive activity, which is an essential requirement for recognizing the patent. And this is so regardless of the fact that the technical procedure for the reproduction or isolation of an element of the human body may constitute an inventive step.

Provisions on Other Biological Materials

The object of the Directive is not limited to the biological components of human origin. So, inventions concerning plants or animals shall be patentable if the technical feasibility of the invention is not confined to a particular plant or animal variety (article 4.2), according to the juridical tradition in this matter.

In accordance with the Directive, microbiological or other technical processes, or a product obtained by means of such a process, are also patentable (article 4.3). This rule is not a novelty either, because it was allowed before under the European Patent Convention. Nevertheless, this recognition is just an exception to the exclusion of the patent of the essentially biological procedures for obtaining plants or animals (article 4.1b). The explanation of this normative lies in that, once the microorganism has been produced, it is capable of natural, fast and abundant self-reproduction or self-multiplication.

Another issue of concern to the breeders is the risk of becoming dependent on the large companies for seeds and livestock improved by genetic procedures. For example, for each new sowing or reproductive period they would have to acquire the corresponding products (for example, seeds or breeding animals), or pay a fee to these companies. This fear has been solved with the so-called "breeder's privilege." According to this privilege, farmers are able to use the products of their harvest for propagation or multiplication on their farms. They are also able to use livestock or reproductive material for the purposes of pursuing their agricultural activity (article 11).

The Public Order Limitation

Regardless of the concurrence or not of the requirements of the patent, the new system excludes from the normative framework those inventions whose commercial exploitation is contrary to public order or morality (the "good customs") (article 6.1). It is an excluding clause that already appeared in the European conventional normative (the Convention of the European Patent of 1973). Although it has never been applied by the Office of European Patents or by any other national court, such an application lack responds to pragmatic reasons and to the difficulty of its application. Although there was an evolution regarding a more flexible concession of the patents, it is always difficult to apply indeterminate juridical concepts such as public order and morality.

The Directive expressly rejects from human biological material: (i) processes for cloning human beings, (ii) processes of modification of the germ line genetic identity of human beings, and (iii) use of human embryos for industrial or commercial purposes (article 6.2).

I have already pointed out (Romeo-Casabona, 2002) the admission of the patent should not be mistaken for its admission or prohibition in another sector of the normative system. That is to say, the processes of cloning human beings is not patentable, but there could be, however, a law that allowed it, or one that prohibited it. It is one thing to allow the activity as such, and quite another to recognize or not the patent of a product or a process resulting from the activity.

With regard to this, it should not be forgotten that the concession of the patent prevents a third party from exploiting the invention for commercial purposes without the authorization or consent of the patent holder.

The Directive contains the following provision, in response to the above issues and the public order clause: "The Commission shall send to the European Parliament and the Council every five years a report on any problems encountered with regard to the relationship between this Directive and international agreements on the protection of human rights to which the Member States have acceded" (article 16 a).

Lastly, and for the same public order reasons, patents will not be granted to processes for modifying the genetic identity of animals that are likely to cause them suffering, without any substantial medical benefit to humans or animals, and also animals resulting from such processes (article 6.2 d).

Pharmaceutical Patents in Developing Countries

Many things concerning patents have radically changed since the entry into force in 1995 of the Trade-Related Intellectual Property Rights (TRIPs), developed by the World Trade Organization. WTO is the only global economic organization with an effective sanctioning capacity, through its Conflict Solution Organ, to the countries for the unfulfillment of its rules. It includes crossed reprisals: for example, a commercial sanction for violating TRIPs. This explains the strange and gnarly presence of the protection of intellectual property in the WTO that reinforces and widens previous agreements. Also it means the generalization from the system of patents to all the technological fields and with a minimum duration of the monopoly of 20 years.

This benefits the large multinational companies of industrial countries that own most of the patents. In fact, TRIPs was developed largely for the benefit of these companies. A dozen large American companies from different sectors, half of them pharmaceutical or biotechnological companies, constituted an Intellectual Property Committee (IPC) with the explicit objective of including the issue on the GATT agenda during the Uruguay Rounds (1986-1994). IPC quickly got the support of the European employer's association (UNICE) and the Japanese Keidanren to pressure the governments. And in 1988 this Triad coalition, without precedents, went to the GATT director and gave him the draft of what, with the support of its governments, became TRIPs.

For most developing countries, TRIPs is a way to harmonize their protective legislation of intellectual property, reaching the level of the most advanced economies. They have a transitory period that ends in 2000 or 2005. For pharmaceutical products, the effective date for most developing countries is 2005, except for those "less developed" (the 49 poorest countries). They initially had one more year and, after the IV Ministerial Conference of WTO in Doha in November 2001, they now have until 2016 for the full application of patents in the pharmaceutical sector.

Industrial country pharmaceutical companies and developing country governments try to rationalize the existing treatments against AIDS. They have already disagreed on several occasions. A well-known case involved the large pharmaceutical multinationals and the Government of South Africa. It was presented in 1998 with the support of the US Government, and retired in 2000, and continued in the US courts until April 2001. The case was well publicized in industrial countries.

However, the Doha agreement did not clarify how developing countries could benefit from that declaration if they do not have a local pharmaceutical industry able to produce medications under an obligatory license, because its import could be in conflict with TRIPs. This explanation should have been done by the WTO before the end of 2002, but there was no agreement. Indeed, despite the important (excessive) surrenders of developing countries, the lack of support of the United States, the European Union, Japan, and Switzerland that defended the interests of their pharmaceutical industry, impeded a consensus solution. In those negotiations, the United States had a particularly rigid position. They tried to limit even more the agreement, restricting it to fewer diseases, but it is to be underlined that the Doha Declaration refers to the protection of "public health" in a general way. And what just before the beginning of the Fifth Minister Conference of the WTO in Cancun in September 2003 appeared as an agreement to facilitate the implementation of the Doha Declaration, now means new obstacles that make it even more difficult to apply.

The hopeful forward step provided in Doha would not have been possible without the campaign of access to essential medications promoted since 1999 by diverse NGOs (nongovernmental organizations). That campaign has had a remarkable impact in the North, and in some international organizations. Among them, the World Health Organization (WHO) includes in its priorities access to generic medications and TRIPs repercussions, although there are some people who consider that it favors commercial companies. It has also resulted in interesting resolutions such as number 2000/7 of the Subcommittee of Human rights of the United Nations, which denounces the negative implications of TRIPs on the rights to food and health. It also affirms the primacy of food and health over economic policies and intellectual property, maintaining that patents on pharmaceutical products should serve social welfare. Resolution 2001/21 of the Commission of the United Nations on Human rights recognizes that access to medications is a

fundamental element for the progressive full realization of the right of everybody to enjoy the highest reachable levels of physical and mental health. It also requires states to ensure that the application of international agreements is compatible with public health.

Because of this, and as the North concentrates the demand on medications and originates most of the benefits of the pharmaceutical industry, the companies retired the demand against South Africa, thus maintaining a good public image. They also accepted the less harmful Declaration of Doha. Nevertheless, we should emphasize that it is a simple interpretation of the Agreement, which has not been changed, exactly what multinationals and industrial countries wanted. In the area of access to medications, there is still much to be done, especially with the incorporation of more restrictive versions of the protection of intellectual property, often called TRIPs-plus. This is present in the negotiations of regional integration agreements as in the case of America's Free Trade Area.

Agreement of August 2003 to Implement Declaration of Doha

In late August 2003, WTO announced a new agreement with developing countries on pharmaceutical product patents. This historic agreement raised hopes among many African countries, and doubts among NGOs, regarding its capacity to help the millions of people with AIDS, malaria, or other infectious diseases. They considered the agreement too complicated and difficult to apply. Through this agreement poor countries can import generic medications to fight more than 20 diseases.

The text had been blocked since December 2002 by some countries–including the USA because they were trying to protect their pharmaceutical industry. After many months of blockage, the 146 countries of WTO allowed the poor countries to import generic medications–which are the same components as patented medications but are much cheaper–to help fight serious public health problems. In this way WTO solved a controversial question just 10 days before the Fifth Ministerial Conference of WTO that took place in Cancun.

Although the agreement received praise, it was criticized by several NGOs for its doubtful practical use due to its complicated mechanism, and the fact that it is not very clear legally. Among the adopted measures, governments that want to import generic medications should demonstrate that they really need the medications, that they have a lack of money to buy patented medications, and that they cannot produce them at the local level. Several clauses have been established to avoid commercialization of generic medications dedicated to poor countries in rich countries, and to avoid their inclusion as generic medicines, some of which are important sources of income for the pharmaceutical industry, including products for obesity and impotence.

The decision will allow countries such as India, Brazil, and South Africa, which have the needed infrastructure for production, to produce patented medications by

pharmaceutical companies from all over the world, if they export them to needy nations.

One of the biggest disagreements referred to diseases that should be included in the agreement's list that allows treatment with generic medications. Although the USA maintained that this would be limited to the treatment of AIDS, malaria, and tuberculosis, others such as the European Commission thought that WHO should decide, if there were any doubts, about the diseases covered by this multilateral mechanism, with the possibility of incorporating any disease in the case of a sanitary emergency defined by the affected country.

Large pharmaceutical companies had argued that such an agreement could relax the normative on the protection of the medication's patents in whose development they had invested billions of dollars. They feared that low-cost producers such as India could find a place to introduce their products into industrial country markets, and use their technologies to their own advantage rather than for humanitarian goals. To address this situation, WTO included a declaration in the agreement saying that countries will only be able to overcome the patents "with good faith and to protect public health … and not as an instrument to achieve industrial or commercial objectives."

The agreement includes certain conditions to guarantee that its final goals are fulfilled. To begin, medications manufactured as generic, and destined to fight epidemics in developing countries, will have a different package and pill color to those used in other countries, to avoid their export to industrial countries. The system includes about 20 diseases, but is reviewed and revised annually.

Legal Position

Patents are being challenged in courts, when they limit access to medications. In February 2004 in Thailand, a court decided to agree with two HIV patients who had maintained Bristol-Myers Squibb blocked their treatment through the rights of industrial property of one of their antiretrovirals. This opened the way for production of generic medications. The court ruled that patents damage the patients, whose health and life depend on whether they can pay for the medications.

The Thai Government produces a series of generics that are 25 times cheaper than the original versions. The treatment against AIDS is different, since these medications are still protected by patents and are too expensive.

It seems that the performance of the NGOs will follow the pace of demands, because in early 2004 Médecins sans Frontières (MSF) accused Merck of breaking the promise made 16 months earlier of reducing to less than a dollar, in poor countries, the antiviral Efiravez (EFV) against AIDS. According to MSF, Merck accepted that discount in a key medication for the combined therapy, mainly for patients with HIV and tuberculosis. However, Merck has not registered it in countries such as South Africa, Malawi, and Nigeria. This means that patients in poor countries

have to continue taking three medications that are 44% more costly than the promised one.

Conclusion

Globalization should provide a way to improve responsibility, solidarity, tolerance, and understanding among nations and people. Problems posed by access to basic and/or vital drugs for developing country needs include:

- Equity of benefits by producers, taking into account that intellectual property rights (patents) can protect inventions, at the same time they prevent access by developing countries and therefore contribute to perpetuating poverty.
- We need to explore some flexible ways to extend ethical concerns for the poor, through voluntary licences, preventing their misuse, or giving medicines free or at reasonable prices for developing countries when endemic diseases are involved.
- Such durable measures are the most desirable ways to close the gap between North and South. To implement North-South interactions, measures could include promoting joint venture projects, improving and funding some local industries (start-up funding), and transferring technology as well as establishing cooperative research programs.
- Good management of resources by authorities of developing countries, even when these are scarce.

References

Bergel, S.D. 2000. La Directiva Europea 98/44/CE sobre la protección jurídica de las invenciones biotecnológicas, Law and the Human Genome Review, 13, 44.

European Group on Ethics in Science and New Technologies to the European Commission. 2003. Opinion Nr 17 on ethical aspects of clinical research in developing countries.

Lema Devesa, C. 1999. Las patentes sobre biotecnología en el Derecho español y en el Derecho comunitario europeo, Anuario de Derecho Industrial, 20, 228.

Nuffield Council on Bioethics. 2002. Report on the Ethics of research related to healthcare in developing countries.

Romeo-Casabona, C.M. 2002. Los genes y sus leyes. El Derecho ante el genoma humano, Cátedra Interuniversitaria Fundación BBVA–Diputación Foral de Bizkaia de Derecho y Genoma Humano–Ed. Comares, Bilbao-Granada.

Chapter 33

Venture Capital, Patents, and the Market: Case Study of Biotechnology in Italy

Claudio Carlone

Introduction

The biotechnology sector has recently returned to the limelight as a result of the notable increase in sales by biotechnology firms in the USA. Estimated annual growth rates are over 20%, a trend that is even more positive in the light of the setback that affected this sector, like others, during the economic crisis that started in 2000.

Biotechnology is gaining more venture capital (VC) in the USA as investors respond to fewer regulatory hurdles for new drugs. Venture capital firms pumped US$3.4 billion into biotechnology start-ups in 2003, up 6.4% from 2002. That gain came as overall VC investments fell nearly 20%. This rise comes as some of the biggest names in traditional technology predict biotechnology will usurp technology in terms of impact (Table 33.1). Biotechnology collected 19.9% of all VC investments in 2003 versus 15% in 2002. Software got 21.9%, down from 24.3% in 2002. One-half of the year's 10 largest VC investments were in biotechnology and other health start-ups.

Table 33.1. Comparing ICT and Biotechnology.

Gene (Locus)	ICT	Biotechnology
Market	Limited by geography	Worldwide
Size	Local and/or regional	Monopoly (US$100 million min.)
Early investment	US$100,000+ to $2million	US$10-15 million
Start-up phase time	6 mos-1 year max.	3 years min.
VC investment strategy	Stay with company and exploit market potential	Leverage position on value and sell with highest return on investment
Impact of regulations	Very limited	Considerable
IP strategy	Selling product, defensive strategy to protect code	No product at VC stage, offensive strategy. Patent

Biotechnology is one of the riskiest industries because start-up costs are especially high–as are failure rates. The median VC investment in biotechnology start-ups in 2003 was US$12.5 million, against US$6.3 million for all start-ups.

Biotechnology is surging in part because the Food and Drug Administration (FDA) is speeding up the drug-approval process. FDA approved 25 new biotechnology drugs in 2003, and 20 in 2002. This speedier approval answers industry and investor complaints that the process takes too long.

Against the performance of listed companies, the biotechnology sector is comfortably outstripping the other market indexes. Since January 1999, NASDAQ's Amex Biotech Index has gained 165%, well above both Standard & Poor's 500 (down 16%), and the Russell 2000 (23%). In 2003 alone, the American index rose by 45%, once again outperforming the other indexes. The highest returns were recorded by highly capitalized companies, which gained an average 54%.

Europe has more biotechnology companies (1900) than the USA (1500), although if we take size, sales, and capitalization into consideration, the "weight" of the European companies is just one-third of that of their American counterparts. At the global level, equity investment in biotechnology companies (including funds collected through the stock exchange) peaked in 2000, at over 31 billion euros (US$23.5 billion–November 2004 exchange rate in this and other conversions), while from 2001 onwards there has been a considerable decrease in the capacity of these companies to attract financial resources (Figure 33.1). At the European level, on the other hand, the trend is strongly positive, with investment amounting to about 1.4 billion euros (US$0.9 billion) in 2001 (Figure 33.2).

This seems strictly related to investments in biotechnology research, as shown by the number of patents as a percentage of national total. According to the OECD Compendium of Patent Statistics, biotechnology patent applications to the European Patent Office (EPO) have been continuously growing over the past 20 years. However, a significant increase occurred from 1993 onwards. Since then, this growth was 14.3% a year, compared with 8.3% for total patent applications. Nevertheless, the ratio of biotechnology patents to total patents is far higher in the USA than in the European Union and Japan (Figures 33.3 and 33.4).

New Zealand, Denmark, and Canada have a high ratio of biotechnology to total patents. In these countries, more then one-tenth of patents relate to biotechnology. In contrast, Italy and South Africa have the lowest ratio of biotechnology to total patents (less than 2%).

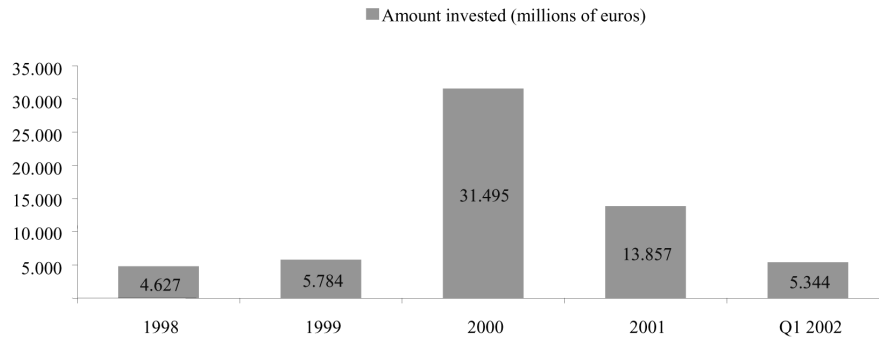


Figure 33.1. Investments in biotechnology companies–historic trend worldwide.
Source: E&Y European Life Science Report 2002

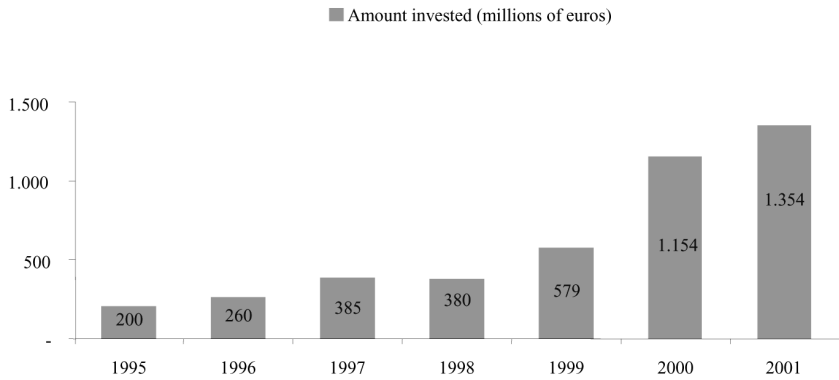


Figure 33.2. Investments in biotechnology companies–historic trend Europe.
Source: E&Y European Life Science Report 2002.

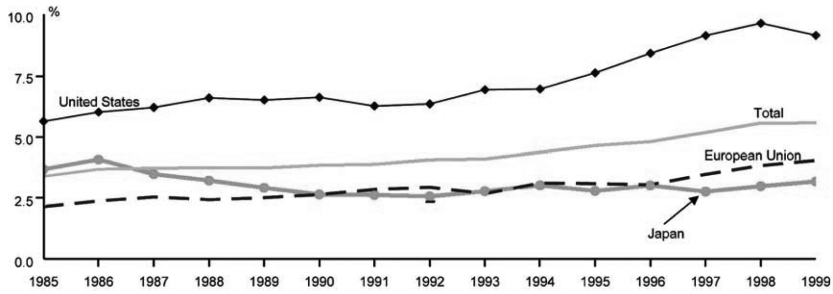


Figure 33.3. Biotechnology patents as a percentage of national total.
Source: OECD Patent Database 2003.

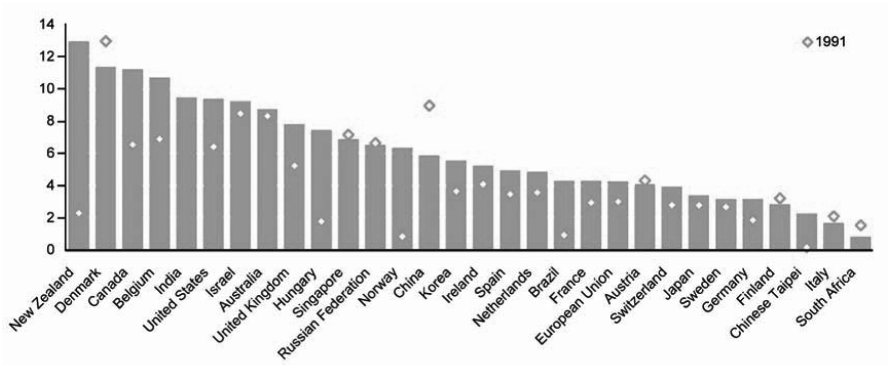


Figure 33.4. Patents in biotechnology: selected countries.
Source: OECD Patent Database 2003.

Biotechnology in Italy

The Italian biotechnology companies listed on the Nuovo Mercato, which amount to 7% of the total, are performing well. Their entry to the market enabled them to raise over 550 million euros, mainly from international investors.

The sequence of acquisitions and mergers recorded in recent years remains unbroken, a sign of good health in the sector and of an interesting process of consolidation and concentration. Nevertheless, if we examine the picture in greater detail, the breakdown by sector of investment in high technology still shows a considerable presence in the ICT (information communication technology) sector (66%). This contrasts with the low focus on biotechnology, which accounts for just 1% of total investment (Figure 33.5).

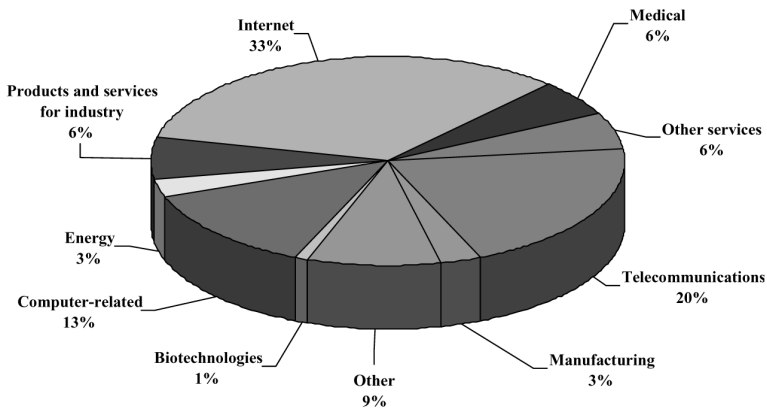


Figure 33.5. Breakdown by sector of amount invested in high technology companies in Italy.
Source: PriceWaterhouseCoopers 2003.

Private investment

In general, after the marked decline in 2001, growth in the Italian market for risk capital seems to have resumed, as it has internationally: 2626 million euros (US$1875 million) were invested in 2002, while the first half of 2003 saw investment of 591 million euros (US$4.22 million), a figure that was set to grow considerably in the second half of the year as a result of a number of large-scale operations.

However, the breakdown of investment by type of operation shows a small and dwindling presence of start-up companies, with investors increasingly focusing on investment in mature companies, for the most part operating in traditional sectors.

An analysis of the percentage of investments in high technology companies shows how expansion and buy-out operations, which account for the lion's share of the market, are almost completely focused on traditional activities.

In general, high technology investments accounted for 20% of the total invested in the first half of 2003 in terms of the number of operations, and 34% in terms of the amount invested. Over the same period, the average investment in high technology companies amounted to 6.7 million euros (US$4.8 million).

In Italy, if we take only private equity and venture capital operations into consideration, the overall amount invested in biotechnology companies has never been particularly high, and indeed has fallen somewhat since 2001.

Lack of investment in biotechnology: the risks

The low number of equity capital operations by companies operating in the biotechnology sector is apparent. In this respect, a number of studies have shown that the founders of new biotechnology companies in Italy refer to difficulties in obtaining start-up funding as the greatest obstacle they encounter in setting up their company.

Investors still seem to find later-stage investment (expansion, buy-out) more attractive than start-ups. Investors begin to show signs of interest at the nearest possible stage to the authorization for sale of the product.

The key problems for investment in start-up companies in the sector are:

- Increasingly strict requirements for the approval of new pharmaceutical products.
- Problems with patenting.
- Lack of specialization by investors.

These factors result in a longer time-to-market, which results in turn in a higher risk for the investment. The risk levels for biotechnology investments are mainly related to the research stage for medicines and the time scales for trials and experimentation, which are too long to enable an objective evaluation of the development prospects of the innovation.

The problems that exist should not lead private Italian equity players to overlook the excellent prospects in the sector. There are numerous factors to attract them. Foremost of these is the demand for increasingly effective pharmaceuticals at increasingly lower costs, as a result of ageing of the population.

Conclusion

There are solutions available to boost investment in the risk capital of biotechnology companies:

- Reduce the time required for the creation and patenting.
- Create public/private risk capital investment funds to finance business start-ups.
- Match demand and supply of equity capital.

- Focus investment instruments on equity capital and specialization of investors.
- Create new privately run business incubators specializing in providing funding and support for new initiatives.
- Enable technology transfer from the universities through patent liaison offices.
- Adopt public incentive programs that do not distort competition.
- Involve the large biotechnology companies in promoting spin-offs.

Analyzing some Italian equity investment experiences, the importance of this form of investment as a growth instrument for biotechnology companies can be clearly seen:

- Vicuron (formerly Biosearch Italia) was established as a result of the acquisition of the Lepetit R&D Centre in Gerenzano through a management buy-out (MBO) in 1996. In 1999 a UK venture capital fund, 3i, acquired an interest in the company, amounting to about 40% of the capital. Vicuron was the first biotechnology company to be listed on the Italian stock exchange: its first appearance in the Nuovo Mercato dates from 31 July 2000.
- Novuspharma was created as a result of the Hoffman La Roche Group's desire to dispose of a research center previously owned by the Boehringer Mannheim Group. Novuspharma S.p.A. was set up on 5 November 1998 through a MBO (management buy-out). In September 1999 the company, which until then had been owned by Hoffman La Roche, was purchased by three venture capital operators: 3i, Atlas Venture, and Sofinnova. After Biosearch Italia, Novuspharma was the second Italian biotechnology company to be listed on the Nuovo Mercato, on 9 November 2000.
- Isagro was established in 1992 through an MBO involving the acquisition of the agropharmaceutical division of Enichem. Isagro is a world leader in crop protection products. It has about 800 employees, 10% of whom are engaged in R&D activities. A subsidiary of Arca Impresa Gestioni SGR and Arca Merchant, it was listed in early 2004 on the STAR segment of Borsa Italiana's Electronic Share Market.

Chapter 34

International Contribution of the Japanese Biotech/Pharmaceutical Industry

Osamu Nagayama

Introduction

In the twenty-first century, known as the "Century of Life," the Japanese Government is strongly focusing on the promotion of Life Sciences and Biotechnology. As part of its economic and fiscal policy, the government set out four strategic research and development areas for investment, with life science as the first. In line with this policy, a document "Biotechnology Strategy Guidelines" was published in December 2002, detailing the basic strategies and measures to which the government should commit itself over the next three to five years. Various measures have already been implemented, with a generous budget allocated to this field. This government promotion should increase opportunities to fund innovation in Japan. It may take time before we begin to see the real benefits. However, the movement itself signifies a huge leap forward, further enabling Japan to contribute to global health and the security of human rights through implementing its highly advanced science and technology.

Biotechnology in Japan

Since modern biotechnology was introduced into the industrial process in the mid 1980s, the biotechnology market has witnessed rapid growth, with remarkable advances being made in life sciences. In Japan alone, the market had reached US$15 billion in 2003. Although the market size represents only 0.3% of the national GDP, we expect to see strong growth over the coming years. Sales of pharmaceutical-related products accounted for one-third of the total Japanese biotechnology market, followed by agriculture/foods and chemicals. As mentioned, Japan is now aggressively promoting the bioindustry as one of the nation's strategic industries, and by 2010 it is projected to grow into a US$200 billion business.

Promotion of biotechnology in Japan is essentially carried out through the cooperative efforts of the government, academia, and industry. The government sets basic promotion policies, and already over 200 measures have been implemented by related ministries. Industries are working closely with the government to achieve rapid applications, and with academia to help maximize their results in basic research.

Japanese Pharmaceutical Industry

The Japan Pharmaceutical Manufacturers Association (JPMA) is an organization of R&D-oriented pharmaceutical companies in Japan. Although the main aim of the JPMA is to contribute to global health through the development of new medicines, it has also carried out some international cooperative activities. JPMA has invited trainees to Japan to study drug quality control, and delegated experts of member companies to participate in technology transfers. These activities have been directed mainly toward Asian countries for the past 15 years. To complement this, JPMA has supplied ASEAN (Association of Southeast Asian Nations) countries with bulk materials to be used as reference substances.

Another Japanese association, the Japan Bioindustry Association (JBA), an organization comprised of bioindustrial companies across industries relating to biotechnology, has been accepting overseas trainees since 1988, to improve biotechnology in developing countries, as well as hosting international meetings to exchange information and technology.

JPMA has also offered its support to tuberculosis control programs in Nepal. As indirect assistance to the project, it provided the anti-tuberculosis drug, Rifampicin, to the Nepalese government free of charge, and helped introduce the necessary manufacturing technology for the drug. In 1988, the Japanese government started a cooperative campaign to rid Nepal of the disease as a part of its ODA activity. However, during this time, drugs became in short supply, threatening the success of the campaign. To remedy this, JPMA shipped over 7 million Rifampicin capsules from 1992 to 1996, which covered both new and relapsed tuberculosis cases during that period. Furthermore, it helped to establish local manufacturing processes by transferring Japanese technology and required know-how. In 1995, local encapsulation commenced, and JPMA began shipping Rifampicin in bulk from 1996 to 1998 in amounts equivalent to that of the previously shipped capsules. In April 1998, the final bulk shipment completed the program, concluding what was generally considered a hugely successful effort in assisting the Nepalese government in distributing the anti-tuberculosis drug throughout the country.

Another example of a collaborative international cooperative program is the “JPMW project,” which began on the initiative of the World Health Organization (WHO). In October 1999 a unique public-private partnership alliance was formed, comprising a number of Japanese pharmaceutical companies, the MHLW (Japanese

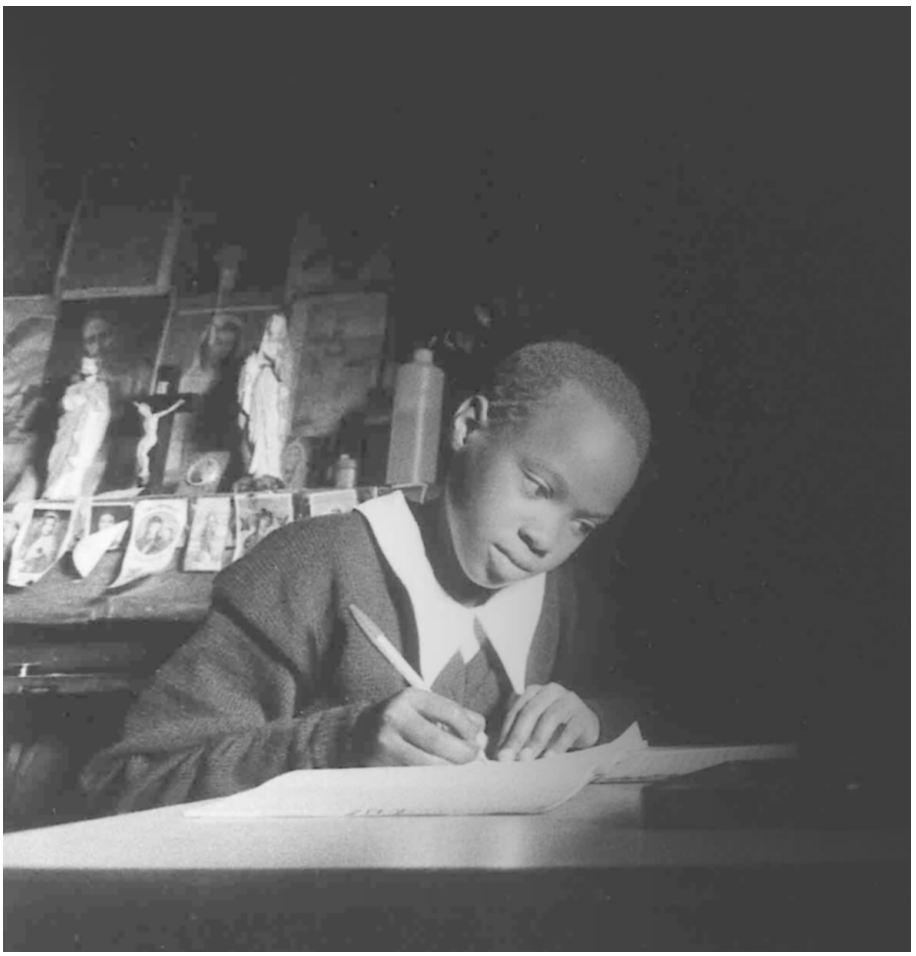
Ministry of Health, Labor and Welfare), and the TDR (The Special Program for Research and Training in Tropical Diseases) of WHO, for the prime purpose of developing new anti-malarial drugs. Currently, 14 Japanese pharmaceutical companies are participating in the project, and have provided compounds for drugs screened by cooperative institutes of WHO with Japanese government funds. As of December 2003, over 25,000 compounds had been screened in vitro assay, and 291 of them were discovered as being potential anti-malarial drug candidates. After further in vivo experiments, 12 were then identified as promising candidates, and a detailed study of those 12 is currently ongoing using in vivo infection and treatment models.

Conclusion

As rapid advances continue to be made in science and technology, it is vital that pharmaceutical industries, especially R&D-based companies in Japan, carry on with the creation of new innovation, technology, information, and knowledge. However, despite the progress made, the reality is that there are still many people in the world who have difficulty in accessing those benefits. To solve these issues, various measures have already been put in place by governments and international organizations such as the United Nations and WHO. We must ensure stronger coordination between these bodies, especially concerning medical issues relating to people and human rights. The pharmaceutical industry will continue its contribution to people across the globe by assisting the government, and by cooperating with the international community.

Section 7

Capacity Building in Life Sciences



Chapter 35

Capacity Building in Science and Technology

Mamphela Ramphele

Introduction

The potential for the life sciences to improve human life is manifest through an increasing number of fascinating discoveries, and the technologies that result. The future is filled with hope for scientific solutions to the problems of poverty, but one question comes to mind: To what extent does science contribute to poverty reduction, and will it be a function not of the rate of change at the frontiers of knowledge, but of the breadth and depth of its absorption worldwide? Moving from poverty to sustainable prosperity will require that science become part of the fabric of society in all countries, as it is today in the wealthiest.

I am heartened by the successes I see around us. Many of our colleagues have witnessed in their own lifetime their countries going from modest hopefuls in the international science community to full-fledged players. The self-reinforcing cycle of economic benefits built on scientific achievement is starting to change these societies. Yet many, many more still linger in fragile and inadequate systems, with no real ability to affect change in their societies.

The main points of the IAC Panel reports (IAC 2004 a.) will find broad support. We believe that science and technology (S&T) has always been an engine of change, and a key determinant of wealth and standard of living. Explicit policy attention, including national S&T development plans, is needed to address the gaps. Human resource development is a cornerstone, and cooperation and collaboration across borders is essential.

Against this backdrop I will highlight several points that should help shape the way we think as we seek to make science and technology a dynamic facet of all societies.

A Single Standard of Scientific and Technological Proficiency

This should be seen as a pre-condition for prosperity–not for a few but prosperity for all. A world in which knowledge is produced in the North for occasional adaptation and consumption in the South is not viable. A single standard is needed so that we stop expecting that countries with no S&T resources can simply adapt the achievements of those where S&T resources are abundant. If healthy populations in scientifically advanced countries rely on an infrastructure of highly-trained physicians, technicians, pharmaceutical researchers, epidemiologists, public health specialists, university developmental geneticists, and qualified high school biology teachers, all with the equipment and resources they need to function, let us not expect that countries lacking these resources can overcome their persistent health problems. Let us instead go about making sure that these scientifically lagging countries have a plan and a path to a future in which they possess the full spectrum of human and physical capital they need in S&T.

Progress can be made from any Starting Point

No country is too poor for science. Any country with the barest conditions of social stability can begin making concrete strides toward improving its scientific and technological prowess. Of course certain types of research are costly and best concentrated at regional centers of excellence. But countries can take many actions to fortify the strength and quality of their efforts in S&T while they wait to accumulate the resources needed for major infrastructure investments. Policy changes that affect the quality of science education, the interactions of industry, academia, and government, or the effectiveness of public action in S&T areas like public health and agriculture can boost the effectiveness of S&T as countries seek greater access to research and other resources.

Migration of Skilled Individuals is a Reality

New research confirms that highly trained individuals are among the most sought after and mobile groups of immigrants. We know that many of the OECD countries set specific policies to compete with other wealthy countries as destinations for health care, information technology, and others skilled labor. Much of this labor has been trained in the developing countries at significant public expense. Moreover, we know that the quality of services in technologically sophisticated fields like health care provision declines to near the point of collapse in the absence of trained workers. Research has found a direct correlation, for example, between the numbers of qualified health workers per 100,000 of population and the ability to achieve adequate vaccination coverage (Brown, 2003). Dealing with the realities of out-

migration of skilled workers means ensuring that the policy agenda includes discussions of responsible immigration policies by receiving countries in the North. But it also means that national plans for S&T in the South must be pragmatic and must consider incentives to minimize the tendency of their most skilled people to migrate.

Science Policy should be Evidence-Based

The availability of robust policy data consistently aids the development of sound science and technology policy. The science community knows that policymakers need constant advice on social and economic benefits that come from strong S&T systems. Scientifically developing and lagging countries have a critical task to build statistical and indicator capacity, as a means of stimulating public debate on the role of S&T. The international development community shares this responsibility as well, when it asks developing countries to help meet the Millennium Development Goals. These goals include child and maternal mortality, and combating HIV/AIDS, malaria, and other diseases. The international community must put resources into their statistical capacity, starting with baseline data and ongoing monitoring and evaluation to document human and physical resources, as a first step in promoting national plans for S&T development.

Education Quality is Crucial

The second Millennium Development Goal is a pledge that by the year 2015 all school-aged children will complete primary education. As the development community is gearing up to make this a reality, the science community needs to gear up as a partner for education quality. We know that getting children in school is only the beginning. Fostering the love of learning and the curiosity that are essential to good science is an equal challenge. As scientists, we must be more vocal in promoting not only schooling, but also quality schooling with dynamic science education for all children.

Information Access must be Affordable

Underlying the specific advances in the life sciences are the revolutionary changes in information technology and instrumentation. Among these, rapid movement and manipulation of information has become the new lifeblood of the modern scientist. Unfortunately, individuals and institutions that can least afford to pay for access to basic information services such as larger bandwidth face some of the highest absolute

costs. Here again the creativity of the scientific community, the development community, and the private sector must come together to find solutions. The scientifically lagging countries of the world have enough challenges in closing the knowledge gaps without being further handicapped by anemic flows of information.

Girls and Women are the Future of Science

Evidence from the United States, where resources for science are not lacking, show increasing disparity between women and men in science and engineering at later points of progression down the career path. Despite reasonable parity in first university degrees and other indicators of gender parity, women account for only 33% of PhDs in science in the US and the UK, and 25% or less in Canada, the Netherlands, Sweden, and Switzerland (U.S. National Science Foundation, 2002). Fortunately, some developing countries have been able to motivate strong participation of women in science, but many have yet to give attention to this issue. Sweden has shown that explicit policies can override the forces that work to keep countries from capitalizing fully on women's potential to contribute to science and technology.

Private Sector is the Engine

Research has documented the contribution of innovation to industrial growth, and the positive effects of improved health on GDP that come from a lower ratio of dependents to working age population, and greater propensity to save for retirement (Bloom et al., 2004a). A 2004 study by researchers at Harvard concluded that one extra year of life expectancy raises the steady-state GDP by 4% (Bloom et al., 2004b). The need for balance and partnership in public and private roles in S&T should not obscure the fact that the demand for scientific and technological knowledge by the private sector is a hallmark of prosperous, high-income societies. Scientifically lagging countries still face lingering obstacles when university graduates see the resource-strained public sector as the only career option, or when industrialists and entrepreneurs fail to grasp the productivity gains that incorporation of knowledge into production can bring.

Collaboration is key

When goals for national S&T development are clear, partnerships can be fashioned to help strengthen the weaker aspects of the system. These should be South/South as well as North/South. When they involve more advanced and less advanced partners,

they should be specifically construed to provide capacity building benefits. Research by the RAND Corporation from 2001 studied developing country collaboration with scientifically advanced countries. It found that the strongest or "proficient" countries had a consistent pattern of coauthorship with an average of five advanced countries, whereas scientifically "lagging" countries (the majority of developing countries) had on average less than one advanced country with which their researchers consistently coauthored articles (Wagner et al., 2001). In examining data from the US, Wagner et al. (2001) also found that when collaboration did take place with lagging countries, it was often characterized as "research about, rather than with, the country." To make progress, we must view every collaborative research as simultaneous opportunity for capacity building.

Centers of Excellence Must Play a Leading Role

Perhaps the characteristic of science which sets it apart from other sociological subsystems is its dedication to evidence-based determination of achievement, and subsequent rewarding of excellence with recognition and additional resources. Contrary to democracy, science thrives on elitism, focusing on the best to benefit the many in society. Putting groups of the best together in adequately resourced centers of excellence has a catalytic effect on the advancement of knowledge. If such centers are structured properly, they are also powerful instruments for advanced training. Sometimes an entire generation of specialists in a given field can result from the intellectual ferment at a given excellent institution. For the developing world especially, such centers can provide the necessary poles around which broader-based capacity building can be nourished. We know that not every country can be a leader in every field, but no region should lack a truly world class center of excellence for the disciplines that are most critical to its development and well being.

Funding Initiatives

Global institutional fund

Soft funding is required for 5-10 years for 20 or more Centers of Excellence – national, regional, nonprogram specific but institution building, to promote the values of sciences, engineering, and medicine and development.

Global program fund–competitive grants

The task for us as the scientific community is to move these messages beyond our own frames of reference and discourse. Amidst the excitement of discovery and the dizzying pace of change in our disciplines, let us plan for an ever-broadening reach of science and technology, so that it benefits and its fascination become truly universal.

Conclusion

Where will we find local expertise with global perspectives and knowledge? Quite simply we must create it throughout the developing countries in vastly greater quantities than we currently do. Over the next two generations, over 90% of population growth will take place in developing countries. The urgency that science uses to accelerate the rate of discovery needs to be harnessed to ensure that its human resource base is made broader and deeper in the parts of the world that need it most. If the conditions can be created where one or two percent of the future's young people have the chance to embrace science as a career, the way the young in OECD countries do, we will be mixing much more hope into the wonder that new discoveries bring.

Hopefully we can draw from Alexandria's past the inspiration for a future where knowledge and its benefits are shared equitably worldwide. For much of the present era, we have grown used to a world in which the most advanced scientific knowledge is concentrated in a small number of countries, many of whose social inheritance was greatly influenced by Western Europe. Until recently, it was too often taken for granted that doing first-rate science meant physically moving to one of these countries, depriving one's native land of the stabilizing influence that an additional great intellectual can bring.

But our cultural memories are short, and we forget that the early intellectual figures of the Western European tradition came to Egypt to get access to advanced knowledge. The Greek Philosopher Plato, dismayed at the political instability in Athens that led to the execution of his teacher Socrates, came to this land around 390 B.C. in what might be described as a prototypical postdoctoral fellowship, or ancient equivalent of a "sandwich" study program. When he returned to Athens years later, he penned an account of the debt that Athenian Civilization owed to Egyptian science and learning. He related how Solon, the Great Athenian Lawmaker, also came to Egypt seeking wisdom and learning. The oldest priest of the City of Sais chided Solon, telling him the Greeks would always be like children because they were unable to preserve the learning that the gods had bestowed upon them.

I know a bit about the dangers that ensue when one culture feels intellectually superior to another; but, in this case, the Egyptian priests sought not to humiliate the young Athenian but to share knowledge with him. He tells Solon that their two great

cities are connected by a glorious and shared intellectual past, wherein they used knowledge to build civilizations that excelled all others in virtue:

> *Our laws from the very first made a study of the whole order of things, extending even to prophecy and the medicine which gives health, out of these divine elements deriving what was needful for human life, and adding every sort of knowledge which was akin to them. [24c]*

As a scientific discipline, health has done much better than prophecy in the ensuing two and a half millennia. But what we are doing today is in the spirit of what the Priest of Sais and the Lawgiver of Athens did in Alexandria in antiquity: looking to the order of nature, selecting what is needful for human life, and struggling to have this guide the laws of our lands. Solon listened well in Egypt, and his ability to transfer and adapt this knowledge brought countless advantages to Classical Athens and the civilizations that followed it. Now let us draw once again on this ancient Egyptian wisdom so that science may bring *"what is needful for human life"* to wherever it is lacking.

References

Bloom, D.E., D. Canning, and D. Jamison. 2004a. Health, Wealth, and Welfare. Finance and Development, p. 10.

Bloom, D.E., D. Canning, and J. Sevilla. 2004b. The effect of Health on Economic Growth: A Production Function Approach. World Development 32(1): 1-13.

Brown, Phylidia. 2003. The Health Service Brain Drain: What Are the Options for Change? GAVI Immunization Focus, October, p. 6.

IAC 2004. Inventing a Better Future: A Strategy for Building Worldwide Capacities in Science and Technology. Full report available at: http://www.interacademycouncil.net.

U.S. National Science Foundation. 2002. Women, Minorities, and Persons with Disabilities in Science and Engineering. Arlington, VA, p. 50, text table 5-3.

Wagner, C. et al. 2001. Scientific and Technology Collaboration: Building Capacity in Developing Countries. RAND, Santa Monica, CA, p. 34-36, figures 3.6-3.8, and p. 3.

Chapter 36

Filling the South-North Gap in Life Sciences and Biotechnology Through Capacity Building, Innovation, and Benefit Sharing

Chen Zhu

Introduction

It is well accepted that life sciences and biotechnology are the major driving forces for the progress of health care, agriculture, and sustainable socioeconomic development in the new century. China, with a population of 1.3 billion, faces tremendous challenges such as population control and ageing, prevention and control of various diseases, water and food supply of good quality, and environmental protection. Being a vast country with diverse natural and geographic conditions, China possesses about 10% of the world's biological resources. Historically China has made great strides in scientific research in medicine and agriculture, which with huge market requirements, provides China with favorable conditions to advance its life sciences and bioeconomy.

However, scientific output and technology innovation in the life sciences and biotechnology are not enough in China. For example, during the period 1992-01, life science related publications accounted for only 19.6% of the total scientific output, compared to 52% globally. According to the World Intellectual Property Organization, patent application numbers reached 113,000 in 2003 through the "Patent Cooperation Treaty" (PCT).

In the United States, from 1990 to 1999, the citation rate increase of the patent-related publications was concentrated on biomedicine and clinical medicine. In 2000, the citation on biomedicine/clinical medicine increased to 60,000/40,000. Together, these two areas covered 70% of the total citations of that year. In contrast, in China, the international patent applications were few. From 1977 to 2001, only about 1200 US patents were from Chinese inventors, and only a small part of these were related to the biomedical field. Facing the fierce worldwide competition of knowledge

innovation, as well as the irreversible tendency of intellectual property rights (IPR) protection, China's infrastructure and mechanisms in R&D formed during the period of centrally planned economy couldn't match the new situation. Therefore, capacity building for science and technology, including life sciences/biotechnology, in China has been considered an urgent task. To fulfill this goal, the scientific community and policymakers agreed that we must develop a sound strategy to increase investment, to carry out structural reorganization, to encourage knowledge and technology innovation, and to strengthen the academia-industry partnership, particularly after the Asian financial crisis of the late 1990s.

The Chinese National Ministry of Science and Technology (MOST) recently proposed Three Strategies (talent, patent, and standard). The Chinese Academy of Sciences (CAS), the nation's comprehensive research center for natural sciences and high technology development, proposed Triple Strategies (leap development, talent, and sustainability). As a result of the support from top-level policymakers and civil society, investment in R&D was significantly increased from 0.64% of the GDP in 1997 (US$ 6.2 billion) to 1.32% of GDP in 2003 (US$18.3 billion).

Currently, the major supporters of R&D activities in life sciences/biotechnology in China include MOST, with its National High Technology Development Program (also called "863" Program, with approximately US$75 million a year for biotechnology) and National Key Basic Research Development Program ("973" in brief, about US$12.5 to 25 million a year for targeted programs in life sciences); the National Natural Science Foundation of China (NSFC, with about one-third of the organization's total funding, or approximately US$80 million a year for life sciences and medical sciences); the CAS (with 15% of the total budget from the State Council, or approximately US$85 million a year); and other agencies of the central and local governments as well as private enterprises.

Major reform programs have been carried out for public sector R&D organizations to identify areas of excellence, to attract outstanding talent, and to establish open and objective evaluation systems. Coordination mechanisms between different research programs and between research institutes/universities/enterprises were also strengthened. A number of national hi-tech parks were built to generate a critical mass for R&D and industrialization. All these endeavors now have started to bring positive results, as reflected in dramatically enhanced scientific output and technology transfer. In 2003, China was ranked fifth in the world for the number of Science Citation Index publications, though the average quality of the papers as judged by the impact factor needs further improvement.

Recent Progress in Life Sciences and Biotechnology

The fact that China is still a developing country dictates that its investment in science and technology be focused on limited but achievable goals. This will facilitate an integration of the national needs with scientific frontiers, take advantage of rich biological resources, and encourage a multidisciplinary approach in R&D.

Basic life sciences

A number of priority areas have been defined after widespread discussion and consultation, including functional genomics and systems biology, bioinformatics and computational/systems biology, identification of genes related to major diseases, molecular biology and biochemistry, cell and developmental biology, neuroscience, systematics, and evolutionary biology.

In the area of genomics, China has already made some internationally recognized contributions. Chinese scientists undertook and completed 1% of the Human Genome sequencing, and contributed to human gene discovery through depositing over 800 novel full-length cDNAs into the public database. Moreover, scientists of the CAS made major progress in rice genome research. They published the draft sequences of the whole indica strain genome, and they have obtained finished sequences of the chromosome 4 of japonica strain as a part of the International Rice Genome Sequencing Project. Recent progress has been made in sequencing the microbial genomes including that of the *Leptospira* interrogans, a pathogen of the tropical disease leptospirosis. In 2003, in fighting against the SARS outbreak, Chinese scientists performed refined analysis of the molecular evolution of the SARS coronavirus. This revealed a positive selection of important viral proteins such as S protein as a result of the virus-host interaction, and also confirmed the trans-species transmission of the virus from the Civet cat to humans.

By taking advantage of the rich human genetic resources, Chinese scientists have made a series of accomplishments in the mapping and cloning of disease-related genes, including those for monogenic diseases such as hearing loss, dentinogenesis imperfecta and familial atrial fibrillation, as well as the loci involved in complex trait disorders such as type II diabetes, essential hypertension, and nasopharyngeal carcinoma. A breakthrough was made in the understanding and targeted therapy of acute promyelocytic leukemia (APL), using retinoic acid and arsenic compounds, making APL the first curable human acute myeloid leukemia.

In fields such as biochemistry and molecular biology, neuroscience, and evolutionary biology, Chinese scientists also made many advances in recent years. For example, scientists revealed the fruit fly's cognition behavior to be similar to higher animal species. In protein science, where China made historic contributions by synthesizing bovine insulin in the 1960s, recent efforts have been focused on the structure-function relationship of proteins. The 3D structure of the 3CL proteinase of SARS coronavirus, a major target for drug development, was resolved. Recently, scientists of the Chinese Academy of Science succeeded in obtaining the crystal structure of the spinach major light-harvesting complex. In the International Human Proteome Project, Chinese scientists are leading the liver proteomics project.

Systematics and biodiversity represent another hot spot in life sciences in China, since these are related to the bioresources and ecosystem protection and hence are extremely important for sustainability. Within CAS, three comprehensive regional botanic gardens (Guangzhou, Wuhan, and Xishuangbanna), now being refurbished,

and nine specialized botanic gardens, constitute the core of a nationwide network for key species conservation. Over 15,000 vascular plant species have been so far collected in these botanic gardens. To promote research on biodiversity, 255 volumes of work (Flora Sinica, Fauna Sinica, and Cryptogamica Sinica) have been completed, which have been widely recognized by international experts.

Major progress in biotechnology

A number of areas have been defined as priority, such as genetic breeding of high-yield agricultural crops, transgenic technology and animal cloning, genetic engineering- based vaccines and drugs, gene therapy, and small molecule drugs based on natural compounds.

Agricultural biotechnology

China has been a leader in hybrid and super-hybrid rice research and application. Recently, scientists have cultivated a group of new combinations of sub-variety hybrid rice with two lines method, having successfully achieved the integration of heterosis and ideal strains. The super-hybrid rice combinations have reached a yield of 12 tonnes/hectares. From 2000 to 2001, the super-hybrid rice was extended to 200,000 hectares. High quality wheat varieties have also been extended. In plant genetic engineering, China has developed several types of transgenic plants such as transgenic storage-tolerance tomato, virus-resistant green pepper, virus-resistant tomato, and pest-resistant cotton. Transgenic cotton now occupies over 50% of cotton cultivation in China, making China the fourth largest cultivator of genetically modified crops in the world. China has also established a biosafety evaluation system. Achievements have been made in R&D of animal biotechnology. Recently, the cloning of animals such as rat, goat, and cow was achieved. In addition, several genetic engineering-based vaccines for livestock and poultry have reached the stage of commercial production.

Biopharmaceutical development

Through many years of effort, the basic conditions have been created for a genetic engineered drug industry in China. In 2002, 18 products were approved to enter the market, 21 products are at phase I and phase II clinical trials, and 35 are at the preclinical stage. The market share for biotechnology drugs/vaccines has been on the rise steadily. For example, the domestic market share for α-interferon made by a Chinese company has reached 60%. The development of therapeutic anti-HBV

vaccines has achieved initial success. Vaccines derived from genetically engineered complex of HBV antigens/antibodies will start clinical trial. The technology of manufacturing artificial blood substitutes was successfully transferred.

A shift is occurring for biotechnology medicines in China from imitation to innovation. Of the top ten biotech-based drugs in the world, China now can produce eight. Research is proceeding for monoclonal antibody or antibody derivatives for diagnosis and targeting therapy. Major progress has been made in anti-angiogenesis therapy, tissue engineering, biochips, and the establishment of human embryonic stem cell lines. Achievements have been made in the development of critical technology for gene therapy. Recently, the State Food and Drug Administration of China approved a gene therapy drug based on p53 in an adenovirus vector, which is the first approved gene therapy product in the world.

China has been making continuous efforts in drug discovery and development based on synthetic and/or natural compounds. For example, Artemether, a derivative of the natural compound Artemesin, has been used as the most effective anti-malaria agent worldwide, particularly among patients who developed resistance to other drugs. Sodium dimercaptosuccinate, an antidote against heavy metal poisoning, was invented by scientists from CAS and is now also used in some Western countries. A number of promising new compounds are under clinical trials, such as Huperzine A, a novel alkaloid capable of improving memory deficiencies in elderly people and those with Alzheimer's disease, and SH1, a cocktail of natural compounds efficient in reducing HIV titers among HIV/AIDS patients. Recently, high-throughput (HT) platform technologies have also been made to speed up drug innovation. For example, the newly established Shanghai National Center for Drug Screening has developed over 200 drug screening assays at molecular and cellular levels, including some HT systems, and has identified dozens of leads with strong activities in some pathways related to cancer and metabolic diseases.

Rapid increase of patent application and market value

In 2002, applications for international patents from the developing countries increased by 11%, with Korea holding 2947, and ranked first, while China ranked second with 1205 applications. The number of domestic patent applications in biotechnology saw a dramatic increase as well over the past few years, from less than 300 in 1999 to almost 2900 in 2002. In 2003, the number of applications for patents in China from residents exceeded for the first time those of nonresidents. The revenue for Chinese biotechnology products increased from US$30 million in 1986 to US$2.5 billion in 2000.

Benefit Sharing and Bioethics

Seizing opportunities to achieve "leap development" has long been considered a strategy for developing countries, to catch up with the world's advanced levels of science and technology. Life sciences and biotechnology are considered as the mainstream of science and technology in the 21st century, and in some of the frontiers such as functional genomics and stem cell research, all countries are at about the same starting point. There is a strong belief that biotechnology may be a key sector in which appropriate development may help to reduce the South-North divide. However, to reach this objective, sincere South-North cooperation is needed. The developing countries must basically rely on themselves to improve capacity building. Investment should be increased in research and education, particularly in areas of key importance such as life sciences and biotechnology. On the other hand, sound national and international policies for the free access to precompetitive data/information/knowledge, such as DNA sequences and protein database, are highly appreciated. It was mainly for this reason that China joined the international Human Genome Project. To this end, a good job must be done in handling the balance between the sharing of genome research results and the protection of IPRs for biopharmaceutical development. The concept of benefit sharing is particularly important in drug discovery/development when human genetic materials and/or natural resources are from developing countries, or when the clinical trials are carried out in these countries. The most ideal model will be the creation of win-win situations in strategic areas of South-North cooperation, so that the human and natural resources of developing countries can be reasonably explored together with the technological and financial resources from the industrial countries.

In promoting the benefit-sharing and South-North cooperation, the solidarity of the scientific community must play a central role, since science is the best way to unite all people across the ideological, socioeconomic, cultural, and historic barriers. All means to facilitate scientific exchanges and technological transfer should be encouraged, such as scientific forums/workshops, training and repatriation programs, joint research projects combining human and natural resources, and expertise on life science and biotechnology. Here, the importance of South-South cooperation in organizing regional or global joint research networks cannot be overemphasized. The international organization UNESCO and international scientific societies such as ICSU, TWAS, IAP and IAC should play leading roles. In addition, with good will and appropriate arrangements, a win-win situation between the international biopharmaceutical industry and local communities in developing countries can also be created to promote health care and biotechnology development. There have been many good stories and experiences in creating joint-venture companies and joint R&D centers. The special de-taxing and price policies that have made anti-HIV/AIDS drugs available for patients in some of the least-developed countries is a good example of government-industry partnership. The participation of industry in capacity building, including training and technology transfer, of the developing countries may open new perspectives.

Compared with other scientific areas, bioscience and biotechnology bears the closest relationship to mankind and our future. While the freedom of the research should be respected, no violation of the dignity of the human being and the universal values of human rights should be accepted. In clinical experiments and the collection of human genetic materials, we should observe the principle of "informed consent." Attention should be paid to the relationship between the development of "predictive medicine" and the protection of individual privacy, adhering to the principle of "informed choice." Great attention should be paid to genetically modified organisms and the related biosafety issues. Stem cell technology development must be in line with the protection of human dignity. All in all, we should encourage cross-disciplinary research and attach attention to the study of the ethical, legal, and societal issues related to the advancement of life sciences and biotechnology.

Conclusion

We are living in a world of economic globalization. Science and technology offer tremendous potential in improving the quality of life and securing sustainable development. However, the gap between the developing and industrial countries is still increasing. We believe that advocating the concept of benefit sharing while enhancing the competitiveness of the developing countries will be the only way to change this unreasonable situation and ensure opportunities of common development. Nothing can replace the efforts of developing countries on their own. China is now a part of the World Trade Organization, so we must respect, learn, understand, and use the international regulations in patent and trade-related affairs, in order to create an international win-win situation.

Meanwhile, the goal of the new generation of Chinese leaders to build a human-oriented, well-off society with coordinated and sustainable socioeconomic development needs the contribution of science and technology. The importance of the life sciences and biotechnology has never been so well understood in China, after the lesson of the SARS outbreak. To keep the momentum of knowledge innovation and valorization of the research in life science-related fields, we need to continue the reform of the research system and to optimize resource allocation. Talent fostering/repatriation should be a long-term policy, and basic science education needs more attention. Intellectual property protection should be further enhanced so that innovation can be encouraged, the competitiveness raised, and the environment for investment secured. We need to deliver sound policy to balance the protection of biodiversity and the sustainable exploration of the biological resources in China. Establishing a value-oriented research management system and enacting appropriate rules and regulations with regard to IPR, biosafety, biosecurity, and bioethics are major tasks of both policymakers and the scientific community.

Finally, we have to continue to promote collaboration with industrial and developing countries, and learn from their experiences in life sciences and biotechnology development.

Chapter 37

Humanitarian Challenges and Global Responsibility and Strategies for Biotechnology

Huanming Yang

Introduction

China is still a developing country, but is facing the challenges of developing and industrial countries. Wenzhou District, for example, has a population of about 7 million, and it possesses 7% of the total wealth of China, according to a recently published report. As one of the areas developing rapidly, it has been built into a society where “most are rich, only a few are richer, and even fewer are poorer.”

With the change of lifestyle and food consumption, together with other factors, the incidence of so-called “civilization-related diseases” has increased steadily in China. Recent reports indicate that the incidence of hypertension has increased to about 11%, diabetes to 6.4%, in the country, and obesity to about 10% in the urban areas.

China still has more than 20 million people living under the official poverty line in relatively undeveloped areas. Meanwhile, one-third of the world’s population is still living on less than US$2 per day.

Health is closely related to food, water, and other environmental conditions. Because of starvation, poor living conditions and healthcare, unclean drinking water, and a deteriorating environment, billions of people are still suffering from “poverty-related” diseases such as infectious epidemics in the industrial countries.

The first global outbreak of SARS (severe acute respiratory syndrome) led to thousands of patients and hundreds of deaths in 2003. The more recent occurrence of avian influenza in Asian countries serves as a warning to us of the new and serious challenges of global health, and further reminds us that all human beings are members of a large family living in a single world.

This global challenge calls for a global response.

Biotechnology: A Response to the Challenges

Biotechnology can contribute to improvement of our health care, revolutionize agriculture through enhanced breeding of livestock and crops, improve pharmaceutical and food industries, and protect the global environment. However, Biotechnology is not a mere technique. It is a part of life sciences and based on genomics, which is at the heart of solving health, food, and environmental problems. Genome sequencing and analysis have provided us with an extraordinary amount of information about life, and has laid down the solid basis for further development of biotechnology.

A Technological or Humanitarian Challenge?

Biotechnology too often seems to be the property or privilege of the industrial countries. Gro Harlem Brundtland, former Director General of the World Health Organization (WHO), stated: “most biotechnology research is now carried out in the industrialized world, and is primarily market-driven. This is ethically unacceptable.”

The Human Genome Project (HGP), one of the great endeavors in the history of natural science, was essentially accomplished in April 2003 as announced by the Heads of Governments of USA, UK, Japan, France, Germany, and China, in the historic “Joint Proclamation” of April 14, 2003.

When we get free access to all the data generated by the HGP, we should not forget that it was in real danger. In 1998, a company was established in the United States with the intention of monopolizing the human genome information, by terminating the internationally collaborated and publicly supported HGP. Equal and free access to the human genome data was the most important and urgent issue in bioethics, because it is related to human solidarity and global harmony.

The world was acting to protect the human genome, the common heritage of mankind. The UK responded by increasing its contribution from one-sixth to one-third. China became the latest contributor to the worldwide sequencing.

As the unique member state in the HGP consortium from the developing world, China’s contribution is not only the technical accomplishment, but also its unswerving effort to protect our genome from being monopolized. The representative from China submitted six proposals to UNESCO’s International Bioethics Committee, which led to UNESCO’s call for free availability of human genome data and to support the HGP consortium.

This call was echoed by the G8 Summit in Okinawa in July 2000 in its communique: *The announcement of the nearly complete mapping of the human genome, a momentous discovery in itself, constitutes a further dramatic and welcome step in this development. We consider this mapping to be critically important for all humanity and call for the further rapid release of all raw fundamental data on human*

DNA sequence as such. This important stand by the international community was also written into the United Nations Millennium Declaration on 19 September 2000: To ensure free access to information on the human genome sequence.

It is a great victory for the whole world, and a great achievement for humanity. We have successfully protected the ultimate principle of freely sharing the most vital knowledge, thus laying the foundation for the global development of biotechnology.

Genomics and biotechnology have developed rapidly in India, Mexico, China, and many other developing countries, thanks to the realization of the importance of biotechnology by authorities and scientists in the developing countries.

In addition to the contribution to the HGP, Chinese scientists have sequenced the rice genome, the major food crop for one-half of the world's people, and the silkworm genome, that is important to the rural economy of many areas. China is also making substantial contributions to the pig and chicken genome sequencing, and many other microbes, in collaboration with Denmark, USA, UK, and other countries. By taking advantage of the established infrastructures, China has enhanced its life sciences and boosted its biotechnology.

As in other developing countries, life sciences and biotechnology in China are still in the early stages. The contribution of developing countries to world science has not been fully acknowledged. The position of developing countries in worldwide biotechnology has not been firmly recognized, and their voices have not been heard. Their access to international resources has been limited by economic, commercial, legal, and ethical frameworks for biotechnology, which were not designed to take account of the needs or the opinions of the developing countries.

EAGLES-Responsible for Global Biotechnology

EAGLES (European Action in Global Life Sciences) is an international consortium of scientists and humanists from both industrial and developing countries. EAGLES sees the global problems related to health care, agriculture, bioindustry, and environment as global humanitarian challenges, and the obligation of life scientists.

Based in Europe, EAGLES calls upon European scientists to fashion a global response, by making the best use of their capacities and resources to contribute to global biotechnology.

EAGLES tries to ensure that Europeans hear the voices of developing countries, to increase public and political awareness in Europe of the needs of the life sciences in developing nations. The group will also do its best to promote science globally, to publicize life sciences in developing countries, and to encourage more contributions to the development of biotechnology by developing country scientists.

We also support the sharing of basic knowledge and international resources of life sciences, and encourage scientists in industrial countries to work in institutions in developing countries, and vice versa.

Chapter 38

European Action in Global Life Sciences

Børge Diderichsen, David McConnell, Huanming Yang, and Marc van Montagu

Introduction

Society must find ways of coping with the awesome consequences of increasing population, food shortages, major diseases and deterioration of the environment that are afflicting many developing countries. Arable land is disappearing due to reconfiguration of climatic patterns, droughts, flooding, and expanding deserts. Poverty is increasing in regions that do not have the resources and the technology to cope with changes in the environment. Transmissible diseases, malnutrition and pollution as well as changes in life styles are threatening human health on a scale never seen before.

Life sciences and biotechnology hold the promise of contributing to meeting some of the fundamental needs for more food and better health facing the developing world as highlighted in the United Nations Development Programme in its 2001 Human Development Report. A growing number of developing countries are now pursuing biotechnologies, and some emerging economies such as China, India, Brazil and Mexico have initiated ambitious national biotechnology development programs. However, there is great variation between countries and regions in their capacities for research and development and in their capacities to meet the onerous regulations now being imposed internationally on the new technologies.

New capabilities should help developing countries reconcile yield increases, sustainable use of natural resources and economic efficiency with social acceptability. Potential applications must be adequately researched and assessed, taking full account of both the environmental safety issues and the needs expressed by the countries concerned to reduce poverty and strengthen food security and nutritional quality, and to develop sustainable solutions for growth with less waste.

Europe's Responsibilities

Europe needs to embrace biotechnology in a wider international context and to respond with responsible and proactive policies at the global level for the strong reason that European decisions regarding life sciences and biotechnology have important consequences on developing countries. Moreover, European life sciences are very highly developed and much more could be done to focus these sciences on the problems of the developing countries. European scientists should be much more involved in research and education programs that are directed at the needs of the developing countries.

In the words of Dr. Ismail Serageldin, chairman of EAGLES, Europe must establish policies that allow European scientists to:

- Engage scientific research in the pressing issues of our time.
- Abolish hunger and reduce poverty.
- Promote a scientific outlook and the values of science.
- Build real partnerships with the scientists in developing countries.

Whilst not compromising food and environmental safety requirements and consumer information policies, Europe should not only provide technical assistance and capacity building but also ensure that its policies do not prevent developing countries from harvesting desired benefits or hinder them from developing life sciences and biotechnology at their own wish and pace.

Europe must therefore integrate the international dimension into all relevant policies, and develop an international agenda, based on fundamental values and long-term objectives, to actively promote balanced and responsible policies globally and in particular toward the developing countries.

As a major player in life sciences and holding influential positions in international deliberations, Europe has a responsibility to help developing countries face the challenges and take up the opportunities of these technologies, and to facilitate the efficient development and use of life sciences and biotechnology in developing countries.

Challenges of the Life Sciences

Great humanitarian challenges for the life sciences lie in illness, starvation, and environmental degradation faced by hundreds of millions of people in many parts of the world. These people suffer from poor health and nutrition while their environment is being destroyed at an alarming rate. Many scientists believe that European life sciences could make a much greater contribution to solving these problems and feel they have a personal responsibility to help. But what can be done and how?

To address these issues and help to make the voice of the developing countries being heard in Europe, the concept of European Action in Global Life Sciences (EAGLES–www.efb-eagles.org) was established in January 2002 with the encouragement of the European Group on Life Sciences (EGLS), a high-level advisory group to the EU Commissioner on Research and of senior officials at the European Commission. EAGLES is supported by the European Federation of Biotechnology (www.efbweb.org) and coordinated by Dr. Ismail Serageldin, Egypt, as chairman and Professors David McConnell and Huanming Yang as vice-chairmen.

The fundamental belief of EAGLES is that biotechnology has a tremendous potential to increase the quality of life and to help steer the world toward a sustainable future. However, in Europe there have been many concerns about biotechnology, and public and political opinion has been focused on risks that are not supported by scientific evidence:

The debate has focused totally on rich consumers and their concerns rather than on what science actually can do.

EAGLES is proposing and implementing information programs that will be carried out mostly by life scientists from developing countries. We believe that these scientists, speaking from direct experience of the problems of the developing countries, can help to allay the concerns of the European public and allow the governments in Europe to mobilize the European life sciences to respond to the needs of developing countries. They will have the authority to contrast the pervasive experience of death and misery in the developing countries with the failure of the industrial countries to use all but a fraction the global resources of the life sciences to bring relief to those who suffer.

Agro/Food

Serageldin (2002) states that 800 million people go hungry and about 40,000 people actually die from hunger or causes related to hunger every day. Meanwhile life scientists in industrial countries have enormous skills and new technologies that could be used to increase food production in what might be called the second green revolution. In the words of Donald Kennedy, editor of Nature, “GM technology may offer the best hope for producing crops on marginal lands that can withstand drought, impoverished soils, and disease.” Yet in Europe these scientists are to a great degree prevented from applying their knowledge to relieving the hunger of the developing countries by poor policies driven by ill-informed public opinion. This cannot go on. We need to respond to Serageldin’s call to become the “new abolitionists” and attack the “new complacency that would turn a blind eye to this silent holocaust which claims tens of thousands of hunger-related deaths every day.”

We need to change the mind of the Europeans concerning their fears of products that have not proven unsafe, and that have been consumed for years by millions of people in the USA and elsewhere. Somehow, Europeans need to realize that GM technology is not only hugely valuable, for example relieving a dangerous shortage of insulin, but it has proved to be one of the safest of all technologies. We have been using the technology for one-third of a century. No deaths or injuries can be ascribed specifically to GM, and no significant damage has been caused to the environment by the use of the technology. Of course all technology carries risks, but we can confidently say, on the basis of experience and from scientific knowledge, that the risks due to GM technology are not *a priori* different from those due to the equivalent non-GM technology. So a new food, say a kiwi fruit produced by GM technology, does not carry any greater risk than the introduction of kiwi fruit produced by classical plant breeding. A new vaccine, say a hepatitis B virus vaccine, produced by GM, does not carry a greater risk than a vaccine produced without GM technology. The use of GM in such projects does not automatically impart any higher risk. In fact scientific information suggests that GM technology carries less risk because it is much more precise than the equivalent non-GM technology. Yet we in Europe are obsessed by the risks of GM technology and we have supported the introduction of international regulations for GM technology that are more onerous than those applied to non-GM technology. The Cartagena Protocol and other regulations may have met the concerns and sensitivities of Europeans, but it is absolutely clear that they are unnecessarily inhibiting the use of GM in developing countries. GM, which has killed nobody and injured nobody, and can save millions of lives, is branded as dangerous by some people and institutions that ought to know better.

In fact GM technology is merely a more powerful adaptation of older well-established technologies. For example, many foods are processed with enzymes. Cheese is produced by rennet, previously made as an extract of the fourth stomach of the calf. Most Europeans are unaware that most cheese today is made with GM rennet, identical to the active agent in traditional rennet, but now made by GM microbes and much purer than the traditional product. GM crops are now being produced by methods that are not different in principle from the methods used by traditional plant breeders for thousands of years, or by plant geneticists in the twentieth century. The new methods are much more precise and cannot be said to be any riskier than the methods of the past. GM is already an integral part of modern European food technology, and carries no exceptional risks that can be ascribed to the role of GM. The evidence shows that GM technology applied to plants and foods is equivalent if not safer and more predictable when it comes to unintended effects on the environment than traditional plant breeding technology.

On the other hand, irrational fear is also real fear. Therefore, “balancing justified caution with acceptance of the benefits that science can bring, is one of the challenges, not just for scientists and food producers, but for society” (Cunningham, 2003).

Europe must overcome its irrational fear and it may be helpful if we in Europe can see what good can be done through biotechnology. It is essential to explain to the European public that there are enormous food problems in the developing countries. Food supply has just about kept up with the growth of the world population, but the growth in food production has slowed from about 2% per annum in the 1980s to about 1% in the 1990s. Hunger is still the normal state for millions of people. The net effect is that there are now more people starving to death and more people living on the edge of starvation than ever before. Biotechnology cannot solve the whole problem of food supply but GM offers new and powerful methods for dealing with specific problems. As one example, we note the case of cassava, an important crop for marginally arid lands. It is the fourth most important source of starch in the world (after rice, maize and wheat) and is extremely important in Africa. There are serious diseases affecting cassava and GM technology can be used to tackle them.

EAGLES believes that the European public will pay attention when eminent scientists from the developing countries point out that:

- There are no sound scientific or socio-economic reasons for fearing the impact of GM technology in their countries.
- GM technology can bring great benefits to their countries and that many scientists will be able to give direct evidence of examples of the value of GM foods in their own countries.

Health

The state of health of millions of people of developing countries is an affront to human decency. Yet most health research in industrial countries is directed at the mostly avoidable diseases of affluence. Meanwhile 20-30 million people die each year from infectious diseases in developing countries. In some cases, such as malaria and trypanosomiasis, the diseases are "tropical". Many tropical diseases are "orphan diseases," meaning that they are no longer the subject of major research programs because they do not matter in the West either to governments or to pharmaceutical companies. The small number of drugs for such diseases were developed during the colonial era when they were needed by the colonial administrations. They are not being replaced by better drugs. In other cases, for example AIDS, the diseases are global but the treatments are generally unavailable or ineffective in developing countries. This situation, in which the West is scarcely using any of the power of the life sciences to relieve the awful diseases of the poverty-stricken developing countries, is totally unacceptable. Life scientists need a new "call to arms," so that they can use their talents to help fight the spectre of death that stalks so many villages and cities in developing countries. We need "to sustain our efforts to reduce human suffering and promote equitable development. We need better tools such as new vaccines, new drugs, and new diagnostics. They must be designed, developed, and

priced to respond to the health needs of the poorest countries." Gro Harlem Brundtland, Director-General, WHO (BioVision, World Life Sciences Forum, February 2001).

As just one example, genomics research will augment our epidemiological and clinical approaches to medical research. Therefore, "it is time for the research community of the richer countries to organize itself such that these benefits can be made available to the poor countries of the world. Otherwise, the fear that the fruits of genomics will widen the gap in health care between rich and poor may become a reality. The question is: "How can we mobilize the skills and resources of the richer countries for the benefit of the health of the developing world?" (Sir David J. Weatherall, Science, October 2003).

Strategy–Focus on Communications

EAGLES believes that the main problems in Europe lie in communications. The public do not understand the scale of hunger and disease in developing countries. They have not been well-informed about the important role the life sciences and biotechnology can play there. At the same time the public have been led to fear biotechnology, which they associate erroneously with risks to health and to the environment, and with socio-economic domination by multinational corporations.

Significant numbers of people have turned against food biotechnology because they wrongly believe that Mad Cow Disease (BSE, CJD), Salmonellosis, Listeriosis and Foot-and Mouth Disease have been caused or exacerbated by biotechnology. Misleading or exaggerated reports of the effects of GM crops on the environment and fears that multinational biotechnology companies are going to undermine traditional farmers have made matters worse. Few people in Europe realize that biotechnology could have a large impact on relieving world hunger. Some people realize that the life scientists now have extraordinary new strategies for developing new drugs and vaccines, and new diagnostic tools, against all diseases. However, few understand how these are developed and much less how they might be developed to deal with illnesses in developing countries.

Consequently, EAGLES wants to increase public awareness in Europe of the needs for responsible applications of the life sciences in developing countries. EAGLES wants to mobilize public and political opinion to guide the EU on how best to fund relevant and effective activities that will be focused on the needs of developing countries.

EAGLES is concerned that some European policies are, unintentionally, damaging to developing countries. We are now familiar with the requirement that all proposals for new industrial or building projects must be accompanied by an "Environmental Impact Statement," which shows how the project will affect the environment. EAGLES proposes that all new European policies be assessed for their impact on developing countries.

We believe that Europe should listen much more carefully to eminent scientists and humanists from developing countries. They are the people who know best the problems, and are best placed to assess the various solutions. They know how European life sciences can be used to help alleviate the problems of hunger, illness and environmental destruction in their own countries. EAGLES plans to provide these authorities with opportunities to influence European public and political opinion and policy.

The authority of EAGLES and its ability to make an impression on politicians, opinion makers, and the media in Europe will rest on the eminence and reputation of its members, especially those who are leading authorities from the developing countries.

As a specific activity, EAGLES wants, when appropriate funding is available, to support young scientists from developing countries who are engaged in endeavors to improve the economic, social, or environmental conditions in their countries through safe applications of biotechnology. As "EAGLES Ambassadors," addressing politicians, civil servants, and the media, these young people could well have an important impact on the European focus and priorities in life sciences.

EAGLES and EU Strategy for Life Sciences

The European Community is committed to finding solutions to the problems of hunger, illness, and environmental degradation, by funding significant research programs. Many people responsible for the European programs would like to see these expanded. Activities suggested by EAGLES will help to implement a number of Actions under the EU Strategy Paper for Life Sciences and Biotechnology 2002 that emphasizes Europe's responsibilities to developing countries and in particular:

- Action 25–the EC should support the establishment of effective research partnerships between public and private research organizations in developing countries and in the EU, and the adequate capacity and infrastructure for developing countries to enter into such partnerships.
- Action 28–the EC should support the safe and effective use of modern biotechnologies in developing countries, based on their autonomous choice and on their national development strategies. The EC should help to ensure that international research on social, economic, and environmental impacts are effectively adapted to take into account conditions prevailing in developing countries, and that international regulatory requirements remain manageable by developing countries, so as not to impede their trade and production prospects.

These intentions of the EU, and the fact that EU is also prepared to pay scientists from developing countries to be involved in EU projects in their own countries, are particularly important since we have to realize that "unless public funding is made

available, some of the most important issues for developing countries may never be tackled" (Donald Kennedy, Nature).

What next?

To achieve these ambitious goals, EAGLES proposes first to establish a platform for outstanding scientists in the life sciences and biotechnology, with the intention of giving voice in Europe to the needs and competencies of these countries. The objective is to mobilize European expertise for the benefit of the poor and needy, for better health, for sustainable development, and for more growth with less waste. These scientists and humanists will be able to advise the European Commission, and indeed national governments, on how to strengthen the global responsibilities of EU programs in education, research, innovation, application, and implementation. The emphasis would be on agriculture and food, diagnosis and treatment of diseases, biodiversity and genetic resources, environment and sustainable development, as well as the safe and responsible use of biotechnology in developing countries.

EAGLES health and agro/food

As a first step to arrive at these goals, EAGLES has applied to the EU 6th Framework Programme for support of an EAGLES Health Communication Programme with the following elements:

- EAGLES Health Communication Office coordinates and stimulates the flow of information about the effect of European health programs and policies on poverty-related disease in developing countries.
- EAGLES Health Lecturers, authoritative experts from developing countries, will lecture, speak and write in Europe, and beyond.
- EAGLES Health Reports will assess the scale and effectiveness of European policies and programs for developing and emerging countries.
- EAGLES Health Symposia will discuss policies and programs.

This Special Support Action has received positive evaluation by the Commission and contract negotiations are currently ongoing. A similar application for EAGLES Agro/Food has been submitted and has received preliminary positive evaluation.

EAGLES Alexandria commitment

During BioVision Alexandria 2004, about 100 participants gathered for an extraordinary EAGLES meeting, and signed the following commitment that had be been prepared by us and the EAGLES Chairman:

- We, members of EAGLES, from the industrial and developing parts of the world, make a joint commitment to work for the benefit of humanity.
- We pledge to motivate the peoples, the institutions, and the governments of Europe to focus and deploy scientific resources to overcome the global challenges of disease, hunger, and environmental degradation.
- We seek to make heard the voice of authoritative scientists, humanists and policymakers of the developing countries, who know and understand the problems of their countries and possible solutions through the use of the life sciences.

Conclusion

At the UN World Summit in Johannesburg, Carlos Rodriquez, Minister of the Environment of Costa Rica, stated that "The globe needs high ambitions and strong commitment. But nobody has the will to do anything about it. Nobody here has dreams on behalf of the world" (Nature, August 2002).

EAGLES believes that scientists, working in concert with others, can have those dreams and that they can realise those dreams and help to steer the world towards a humane and sustainable future for all people.

References

Cunningham, Patrick. 2003. Towards Sustainable Agriculture for Developing Countries. European Commission Conference, Trinity College, Ireland, January 2003.

Serageldin, I. 2002. World Poverty and Hunger–The Challenge for Science. Science, 296: 54-58.

Serageldin, I. 2003. Towards Sustainable Agriculture for Developing Countries. European Commission Conference, Trinity College, Ireland, January 2003.

Section 8

BioVision Alexandria 2004

Chapter 39

An Overview of BioVision Alexandria 2004

Rafik Nakhla, Cynthia Schneider, Salah Soliman, Frederic H. Erbisch

Health Care and the Poor

Rafik Nakhla

"A healthy world is dependent on our ability to put modern technology to the service of developing countries."

Infectious diseases represent an enduring threat to the developing world. Only 10% of global health expenditure impacts 90% of the people. This disparity is evident in food distribution where 80% goes to 20% of the global population. The divide will be also witnessed in the type of diseases affecting the population, with developing countries continuing to be plagued by infectious diseases, and the industrial countries will suffer from a quite different group of diseases related to aging, as life expectancy approaches 100 years in some countries.

Two diseases affect all humans: cancer and HIV/AIDS. If diseases of the industrial north are related to ageing, and the developing world continues to suffer from parasitic and infectious diseases, the pharmaceutical industry will focus on certain diseases while neglecting others such as malaria, schistosomiasis, filariasis, diarrhea, hepatitis C, and intestinal parasites. For example, the pharmaceutical industry developed 1400 new medicines over the past 10 years, only 14 of which were for diseases affecting primarily poor people.

Major Diseases

HIV/AIDS

HIV/AIDS is an emergency and a long-term issue. Despite increased funding, political commitment, and progress in expanding access to HIV treatment, the AIDS epidemic continues to outpace the global response. The AIDS epidemic has undermined the benefits achieved by health care in Africa, and life expectancy has now fallen by 10 years.

The African AIDS is different from the epidemic in North America and Europe. In the latter, it is limited to some high-risk groups, and its control is possible through intensive education, vigorous political action, and expensive drug therapy. In Africa the disease has killed society's fittest, leaving the old and the children behind. One cannot define risk groups: everyone who is sexually active is at risk.

Africa is home to just over 10% of the world's population, yet almost two-thirds of its people are living with HIV. In 2003, an estimated 3 million more people became infected and 2.2 million died (75% of the 3 million AIDS deaths globally that year). AIDS is also intensifying chronic food shortages in many countries, where large numbers of people are already undernourished. The epidemic is significantly reducing the agricultural workforce and family income.

Malaria

Malaria presents several challenges due to its endemic nature to sub-Saharan Africa, where 90% of cases develop. Over 300 million cases of malaria develop each year, with its main victims children under five. Malaria causes more than 1 million deaths, 90% of which occur in sub-Saharan Africa. Malaria is highly debilitating, reducing productivity of sufferers, which has a direct impact on economic growth. It is mainly a disease of the poor, and it compounds poverty.

Sleeping sickness

Trypanosomiasis or African Sleeping Sickness affects 300,000-500,000 people every year, and has a severe negative economic impact. It kills about 3.5 million cattle yearly with a further 46 million cattle at risk and precluded from certain parts of Africa infested by tsetse flies. However, this is truly an orphan disease that is treated with a 50-year-old drug Melarsoprol. This toxic drug is a derivative of arsenic. The disease is spread by the tsetse flies that inoculate the blood stream with the parasite.

There are major restrictions to developing new drugs for this serious disease, including lack of funding, lack of interest, lack of understanding of the problem, and lack of focus on suitable solutions, and lack of communication and understanding between the different parties interested and working in these areas.

Tuberculosis

Tuberculosis (TB) is the most important killer of people in the fertile working age range, despite the fact that it is mostly treatable at reasonable cost. TB affects 10 million people and kills more than 2 million people yearly. It is complicated by being often combined with HIV/AIDS. Eradicating TB requires improved treatment and the development of new diagnostic tests and new drugs. Health care strategies should emphasize prevention through new vaccines and treatment of latent infections.

Cancer

There are 10 million new cases of cancer and 6 million deaths every year. These numbers are expected to grow by 50% by 2020. Cancer is a disease of the poor as well as the rich. Underlying causes for the wealthier countries include diet and obesity, whereas the poor suffer through poor storage of crops that infect them with carcinogenic toxins from fungi that grow on these food crops.

Changing habits can have a dramatic effect in reducing the incidence of various cancers. For example, lung cancer can be largely prevented by avoiding smoking. Good preservation of an important crop such as peanuts also can prevent the presence of aflatoxin, a highly carcinogenic material that is implicated in liver cancer. Aflatoxin is produced by fungi that grow on peanuts if they are not preserved properly.

Almost all cancers of the cervix are linked to sexually transmitted papillomavirus infections, and the use of condoms can reduce the incidence dramatically. The incidence of prostate cancer can be reduced by eating certain foodstuffs that contain powerful antioxidants such as lycopene found in tomatoes. Selenium also had a positive effect, reducing incidence by 66% after treatment for 5 years. The third element was Vitamin E, which reduced incidence and mortality by 40% in a double blind randomized Finnish study.

Prevention of infectious diseases

Prevention of infectious disease in most cases requires more radical measures in two areas: public health and vaccination, in addition to the change of diet and habits.

Public health

Public health includes access to clean water, effective sewage disposal, and food hygiene that is imperative to prevent liver cancer in Africa. Sexual hygiene, especially using condoms, has been the focus of AIDS prevention.

The banning of DDT for its hazardous and toxic effects had a negative effect on the control of vectors, such as tsetse fly that spreads sleeping sickness (trypanosomiasis) and the anopheles mosquito, the vector of malaria. Uganda is considering reintroducing DDT for use inside houses to control mosquitoes. These two insects spread two major diseases in Africa.

Vaccination

Vaccines have significantly reduced incidence of some infectious diseases by 98-99%. Vaccination also led to the global eradication of smallpox. Despite these successes, vaccines are still unavailable for malaria, HIV/AIDS, and other orphan diseases.

Recent vaccine scares among the public present serious problems. An example is the article by Edward Hooper who said the polio vaccine spreads AIDS, although there is no supporting evidence, and studies have proven the opposite. Public concern and resistance to mass vaccination resulted. Despite the established benefit of vaccination, mass vaccination has always been attacked based on the precautionary principle that states:

> *"When an activity raises threats of serious or irreversible harm to human health or the environment, precautionary measures that prevent the possibility of harm (for example, moratorium, prohibition) shall be taken even if the causal link between the activity and the possible harm has not been proven or the causal link is weak and the harm is unlikely to occur."*
>
> *This principle has been contested particularly in medicine and public health. Sir Peter Lachmann states an important principle to counteract the precautionary principle when he says:*
>
> *Particularly in medicine and public health, it is very doubtful whether it is ethically preferable to do harm by omission rather than commission. The precautionary principle is therefore no substitute for rigorous risk benefit assessment of all courses of action–including doing nothing.*

Agriculture and Safe Food Sufficiency

Cynthia Schneider

Issues

The key themes today are the burden of the regulatory process, and the growing gap in attitudes and adoption of biotechnology between North and South. At Biovision Alexandria 2002, the chief obstacle identified to realizing the potential of science for developing countries was weak infrastructure–capacity, government, finance, education, and transportation. In 2004, the chief obstacles identified were the "extreme cautionary approach to applications of biotechnology in food" and cost and bureaucracy of the regulatory processes worldwide.

Caution is costly. Current regulatory processes are delaying access to potentially useful technologies, with serious consequences to those who may benefit from these applications in food and agriculture.

Applications

Science is offering successful solutions. For example, the Agriculture and Biotechnology Support Project (ASBP ll) at Cornell University developed a fruit and shoot borer-resistant eggplant (FSBR) that will reduce crop loss (up to 54-70%), and reduce pesticide use. Estimated yearly economic gain is US$164 million. There can be affordable food for millions, but it takes from 6 to 13 years for a transgenic plant to reach commercial release.

Livestock Diseases

In animal agriculture, there are many obstacles: of 1300 drugs developed, only 1% are for tropical diseases; theileriosis and east coast fever put 24 million cattle at risk, leading to 1 million deaths yearly at a cost of US$130 million. This situation extends across 11 African countries. The pathogens need to be sequenced and we need this knowledge for vaccine development. If there is not investment, there will be no vaccines for tropical livestock diseases.

Bringing Products to Market

There are many challenges for public and academic institutions to bring products to market: the high cost of R&D, with the public sector inexperienced in the "D"; high transaction costs; the regulatory environment is hostile; and funding is scarce. The question of indemnification is critical. What if a client country accepts a product without a U.S.A or European regulatory seal of approval? This could be dangerous because of a possible lawsuit. An action plan could involve: having the public sector of Life Sciences present at relevant policy platforms. It also needs organized representation of the scientific community as a stakeholder group, and attending treaty and protocol meetings, and speaking up early in the process. Alliances with like-minded environmental activities would also be helpful.

What are the consequences of absence of life sciences from the debate? Cartagena protocol requires permits to bring newly developed GM crops into developing countries. So if a student on a fellowship developed a product in Europe, there would be restrictions on bringing it back? The reality is that agriculture policy is being decided in environmental forums. Without innovation policy, regulation becomes policy. Upcoming events that will address important issues include the 2007 Cartagena decision on liability; The World Food Summit: harness technology to increase food security.

Lessons Learned and Actions Required

- Communicate early and often.
- Complement local efforts.
- Focus on delivering products.
- Create institutional partnerships through products.
- Consider a different paradigm for risk/benefit calculation that takes into account risk from NOT developing a product?
- A different indemnification model could be based on national government indemnification for works of art on loan for exhibitions.
- Orphan crops legislation needed that is comparable to orphan drugs, to stimulate R&D activities.

Exploiting Biodiversity and Protecting the Environment

Salah Soliman

Effects of Climate Change on Biodiversity

We need to understand the effects of environmental changes on biodiversity. It is important to determine the nature of the changes and where, when, and at what rate they occur. By applying remote sensing techniques, particularly photographing the earth from space platforms, much can be learned and changes can be monitored. Unmanned imaging satellites 600-1000 km above the earth collect and transmit images that provide greater detail than is possible from the high-altitude satellites. Images obtained by these systems are useful tools in monitoring the environment. Meteorological satellites helped in understanding global weather patterns and the effects of local events on them. Medium resolution images are used to record and measure the effects of phenomena such as hurricanes and forest fires in vegetated areas, waging war in desert regions, and oil spills in the oceans. High-resolution images provide details of environmental parameters that affect ecosystems and pinpoint sources of pollution whether natural or caused by humans.

Biodiversity Deterioration, Its Causes and Solutions

Intensive agriculture has negative impacts on species and genetic biodiversity within agricultural systems, primarily due to low crop and structural diversity, and through the use of pesticides and tillage. The impact of intensive agriculture on biodiversity primarily stems from conversion of natural habitats into agricultural production areas by use of irrigation. The transport of fertilizer and pesticide residues into rivers and lakes also causes significant habitat deterioration through eutrofication and toxicity. The challenges faced include:

- Increasing crop production to meet population growth.
- Improving crop and genetic diversity crucial for increased productivity, and for increased resistance to abiotic stress.
- Increasing knowledge.
- Identifying, measuring, and monitoring problems and changes.
- Identifying problems and areas of vulnerability.

The following solutions are proposed to address these challenges:

- Increasing the efficiency of agricultural production can reduce these impacts, as can minimizing off-site movement of fertilizers and pesticides.
- Using technologies, such as genetically modifying crops, may also play an important role in solving part of the problem.
- Creating agricultural systems with lower impact on biodiversity and maintenance of high levels of biodiversity.
- Using available technologies while simultaneously encouraging appropriate biodiversity-friendly farmer practices.

Traditional and new practices are important, and the integration of this knowledge of the agriculture biodiversity should cover crops, livestock, soil biota, pollinators, pest and pathogens, and predators. They can then be used as indicators of diversity change and in assessment of gene flow. We can upgrade the use of diversity through improved gene bank management, using high throughput tools for characterization, using local wild species in breeding, defining genetic erosion baselines, creating networks of existing genomic projects, and encouraging functional genomics and allele-mining strategies.

To improve our understanding of biodiversity and ecosystems, we need to focus on contributions to ecosystem services (watershed management, nutrient cycling), the nature and distribution of below-ground biodiversity, interaction of on-farm diversity with wider ecosystem diversity, and crop diversity as part of integrated pest management.

To highlight the economic output of biodiversity, we must determine its economic value, and evaluate the equity of cost-sharing across society, to encourage farmers to adopt good biodiversity management practices.

It is important to optimize agricultural biodiversity for higher productivity and food security, and human and environmental well-being. To accomplish these aims, diversity must be protected and maintained, while promoting the value of underutilized species, and adopting useful policies and incentive approaches. We also need to narrow the knowledge gap in evaluating and protecting agricultural biodiversity. The overall message is a confident one: science has tools to help us solve the issues, and will help us invent appropriate tools.

Tree Biodiversity as a Special Case

- Biodiversity is vital to sustain forests.
- Genetic diversity of trees is less well known than for other plants, but may be vitally important for a future where demands for wood will increase, putting even greater pressure on our natural forests.
- Contribution to the difficult area of defining and measuring genetic diversity.

- Significant contribution to ecotourism, for example in Costa Rica.
- Dryland biodiversity–dryland ecosystems are important not only to those who live there but to all of us, especially as they hold very high genetic diversity. There are frightening trends in degradation of these areas, mostly from human activities.
- The long-term hope of success is harnessing indigenous knowledge, scientific information, and the will and skill of the people who live in areas rich in agrobiodiversity, and by using indigenous spices, landraces, and genetic resources, complete with intelligent use of land and water that are key ingredients of life.

Patents and Biodiversity

Mutual cooperation between local small institutions and global corporations could result in saving biodiversity and in bringing equitable benefit to industrial countries.

For example, in a case study from Brazil the key role was to integrate efforts, resources, traditional knowledge, and local research results of the public experience, academia, and national development groups to create fair cooperative agreements with international clients. The vital point in making this work is that access to biodiversity should be allowed only through legal contracts. The cost for R&D in the Brazilian example was lower than that in industrial countries, but can be financed only through mutual cooperation.

An interesting example of open source technology is DArT: Diversity Arrays Technology (DArT) was developed in Australia based on a principle to differentiate between fragments specific for some individuals and those common to all. DArT markers are defined as DNA segments, which are present or absent depending on the individual genotype. DArT works with a molecular base response to changes that cause the defined segment to be present or absent, and they can be located anywhere in the genome. DArT markers could be used in whole-genome fingerprints, diversity analysis, or genetic analysis. They have been used and proven useful in barley and rice. Some other crops are being studied. DArT is particularly of interest to orphan crops because it does not require sequence information.

Trade, Patents, and Developing Countries

Frederic H. Erbisch

The conference participants were challenged to use their imagination to develop novel and better means to deal with intellectual properties, to meet private and public sector interests, and especially to serve society. This challenge should not go unanswered. The present intellectual property protection system was developed long ago, and has been adequate for many years, but the results of biotechnology research are much different from the products developed by engineers and chemists, the products the system was designed to protect. The products of the new science, biotechnology, certainly need to be properly protected, but is this "old" system really adequate to do this? The question is, should "new wine be put into old bottles?" The new system should provide protection for the innovator and it must also consider how to properly provide for society. The challenge has been made, now it is time to be imaginative and creative.

Types of Protection

Generally, when speaking of intellectual property rights (IPRs), one immediately thinks "patents." However, there are other protection systems such as copyright, trade and service marks, and plant variety protections. In a sense, these are "traditional" protection systems. These systems provide protection for innovations created by people. More recently, biological resources were given national protection through the ratification of the Convention on Biological Diversity (CBD). With the CBD in place, biological resources and natural resources have an owner. This gives a state and a country the right to exploit its own resources. Under the CBD, access to genetic resources is the right of the country and the country makes these resources available under its own terms.

Another treaty, the FAO-based Plant Genetic Resources for Food and Agriculture (PGRFA), has rights similar to those of CBD. The PGRFA document states: "Others are required to recognize the sovereign rights of states over their plant genetic resources for food and agriculture" (Article 10).

Those new systems, CBD and PGRFA, appear to adversely affect biotechnology research and bioprospecting because of potential liabilities problems. The main liability would be the loss of a researcher's and/or company's reputation, such as being charged with biopiracy. Because of the protection offered by these two treaties some developing countries believe their resources are so important that

biotechnology cannot progress without their resources. Believing this, these countries might ask for unreasonable terms and conditions when sharing these resources (the resource-rich South vs. the resource-poor North). However, this is a dangerous position to take because the North is also rich in biodiversity and could use these resources instead, which could deprive the South of needed financial assistance.

Ethical Considerations

Ethical considerations are important whenever addressing various aspects of obtaining or transferring protected and/or unprotected intellectual properties. These ethical considerations apply to all North to South, South to North, South to South, and North to North transactions. It is important that developing countries create their own ethical conclusions, and for the industrial countries to respect and act upon these ethics. The industrial countries need not and should not impose directly or indirectly their ethical standards on developing countries, or create an ethics system for them. Global respect for the ethics of others will improve responsibility in intellectual matters, build understanding, and reduce intolerance. It could also provide for good management of resources, provide benefits throughout society, and open markets throughout the world.

Hunger and poverty are two items for ethical considerations. The number of hungry people in developing countries has generally decreased in the period from 1969 to 1998. Data showed that two factors, lowering food prices and increasing plant growth, could reduce hunger considerably but not completely by 2025. It would take an additional 25 years to feed everyone properly. Here is a problem: knowing it will take approximately 45 years to achieve the goal of "no hunger," is it ethical to provide only short-term research or other types of support, say 2-5 years, or is it more ethical to provide long-term support? Short-term support will help to some extent, but will it be enough? Could changes in the way of handling intellectual properties help this situation? Should the way(s) in which intellectual properties are handled be changed to better serve society be considered as an ethical consideration that must or should be addressed?

Patent laws and Trade Related Aspects of Intellectual Property Rights (TRIPs) documentation include a number of ethical considerations. For example, those inventions that are contrary to public order or morality are not patentable. TRIPs provides the means for developing countries to harmonize intellectual property legislation. Also, the Doha Declaration of 2003 allows for the importation of patented drugs for more than 20 diseases to certain developing countries, and allows developing countries with production capabilities to produce patented drugs and distribute them to other developing countries. Although patenting is still the best way to protect inventions, including medicines, it is imperative to search for ways to

provide exceptions to the patenting system to ensure that the poorest countries have access to critically needed medicines.

The People's Republic of China as a Case Study

China has made great progress in biotechnological research by increasing investments in research, building research capability, strengthening research partnerships, and structurally reorganizing life sciences research facilities and institutions. The results in biotechnology advances have been great, and include significant contributions to the identification of the human genome, complete identification of the Indica rice genome, gene identification of a number of major diseases, and the mapping of a number of disease vectors. As a result of all these efforts, patent application in 2003 has increased, and for the first time the number of resident applications exceeds nonresident ones.

In addition to building China's capabilities and increasing intellectual property output, it appears that the increase in biotechnology research has decreased the South-North division. With this progress other benefits of biotechnological research could arise, such as the creation of win-win relationships through South-North cooperative research programs, development of a global research network, a means of sharing expertise, reagents, etc., in South-South research relationships, and the building of human dignity. The development of biotechnology research capabilities in other developing countries could also follow China's pattern of success.

Start-up Company Support

One of the results of biotechnology research is the establishment of start-up companies, based on biotechnological innovations. In addition to an innovation, a start-up company needs financial support and these needs are great. A biotechnology start-up company may need US$10-15 million during the initial three-year start-up phase. Because of patenting situations and numerous regulatory requirements, it may be several years after the initial start-up phase before a marketable product is produced by a new company. In contrast, a non-biotechnology start-up company may only need US$100,000 to US$2 million to complete a much shorter initial start-up period, six months to a year, and have a product in the marketplace shortly thereafter.

In industrial countries, financing for start-up companies is difficult to obtain. Without financial assistance the company will not have a chance to develop. Venture capitalists often provide the support needed for the start-up. These investors prefer to provide funds only after the start-up has gone through a number of initial steps of formation and product development. Usually the investor requires a substantial share of the company (equity) and control of the company's management when investing.

A number of suggestions to increase the chances of receiving start-up support have been made and include: reduction of the times for obtaining patent protection and obtaining regulatory approvals, creation of public-private risk capital investment funds, creation of new privately run business incubators specializing in providing support for new entities, adoption of public incentive programs, and involvement of the large biotechnology companies in promoting spin-offs and supporting start-ups.

As developing countries continue to build their biotechnology research programs, it is expected that they will discover innovations that could form the basis for start-up companies. If financing is an important aspect of building a start-up company, and this funding is difficult to obtain in the North, will there be funds available for the developing country start-up? Is it practical to even try to put the above-listed suggestions for the North in place in developing countries to aid potential start-up companies? So the question is, who will support the start-up companies in the South? Also, where will the specialized management personnel needed for start-ups be found in these developing countries? The North and the South need to study this issue of biotechnology start-ups to discover how the South can take advantage of its biotechnology findings and initiate the formation of new companies, companies that will provide opportunities for employment, for the production of products for its own people, and for the generation of revenue to support itself. These companies could become major factors in the future development of the South.

Intellectual Property Concerns

Although the handling of patentable and patented innovations has received primary consideration, the South and the North will have to address other intellectual problem situations. For example, the rapid and extensive development of digital technologies has endangered the traditional copyright system–the digital revolution. Copyright protection involves controlling the copying of written materials, of music, and other such creations. But can this be done now? Copying of music, papers, books, and other creations is easy to do digitally. And it can be done almost anywhere in the world. The question is: How can the copyright law be enforced under these conditions?

Through the Internet, one of the products of the digital revolution, one can do numerous searches for information quickly and easily. Resource materials become easily accessible through the Internet. Materials can be downloaded for use, they can be copied for use by others, and they can be shared with others. This especially benefits developing countries, giving them immediate access to libraries throughout the world to research literature and assistance. They do not have to wait for written materials to be sent to them, nor are they denied access because of where they work or live–distance is no longer a problem. The researchers of the North also have these advantages. But what about the innovator, the one who creates the materials being freely used by everyone everywhere in the world? What is the innovator's reward?

What incentive will the innovator have to continue innovating? Will researchers be encouraged to publish their findings on the Internet? Will scientific journals become a thing of the past? What happens to the "publish or perish" requirement of research universities? What about peer reviewed research reports and journal articles? Instant publication precludes outside review. Will the digital revolution affect the patent system and the distribution of its products as in biotechnology research, and what considerations will need to be made to prevent unequal distribution of the results of digital age efforts? All these questions and many more need to be addressed by both the South and North in a very timely manner–it is happening now–is the world ready?

Biotechnology Safety

There are a number of other associated concerns relating to intellectual properties, their protection and management. One of these concerns deals with the safety of biotechnological products such as genetically modified organisms (GMOs). The record of safety for biotechnological products is extremely good, actually being an incredibly low-risk area. The 30-year record of biotechnology shows no deaths, no injuries, and no damage to the environment. The problems related to GMOs result more from misconceptions and misperceptions in the public sector. It is, and will be, necessary to continue discussing with the public the safety of GMOs and other biotechnological products. This matter must concern the South and the North, because strong objections and/or fears could prevent the use of a valuable product anywhere and everywhere in the world. This may just be an inconvenience in the industrial countries, with many alternatives, so not having a particular product may not cause a hardship because an alternative product could be used. In developing countries, however, there may be no alternative or substitute product, and nothing will be available, perhaps causing considerable hardship for the people and lack of access to potential benefits.

Use of Intellectual Properties

Suppose there were no restrictions on the use of intellectual property, no IPR, or no enforcement of IPR. Would and could developing countries take advantage of this opportunity? Many developing countries could not take advantage of freely available intellectual property, especially in the biotechnology area, because of the lack of trained biotechnology researchers, equipment, and associated materials. In a sense much of the North's protected intellectual property is available now to most of the South because jurisdictional protection for innovations does not extend to these countries. However, before it is possible to use this technology it is necessary for the developing countries to first get their policies, laws, and research programs in place.

Adaptive biotechnology research capability is the ability to take biotechnologies and adapt them to conditions within a country. If the developing countries do not have this capability they certainly would not be able to take advantage of intellectual properties available to them now. As federal patent protection expires, patented technologies become available. There are a number of expired biotechnology patents presently available. Are they being used in developing countries? Is non-use because the developing countries only want to develop patentable products, or is it because the infrastructure needed to use these available innovations is not in place? Perhaps as, or more, important than the necessity of having available biotechnologies is the development of the appropriate infrastructure of research capability, research facilities, and laws for developing countries to build biotechnology research programs, and subsequently develop products to benefit society.

Other Considerations

The major agricultural biotechnology firms are careful when using various types of biotechnology tools and materials such as genetic materials. These companies follow all regulations, do considerable testing, and do not release any new products until they have received approval from national government agencies. At the present time these companies can restrict the use of these biotechnology materials because the materials are under government protection, generally patent protection. When these materials become freely available, that is when all patent protection has expired, who will be responsible for the continued safe use of these materials? Who will be responsible for any problems caused through the use of these "free" innovations? Industrial and developing countries must address this situation of responsibility for the use of unprotected biotechnological innovations.

In industrial countries biotechnology innovations are often highly evaluated and considered quite valuable. What about in developing countries? How are innovations valued? Do some think that because an innovation comes from a developing country it is not worth as much as one from an industrial country? Does the location of an innovation or discovery determine how an innovation is to be used? Does it determine its value?

Some have suggested that for the sake of humanity, a global moral obligation, companies owning certain intellectual properties should make these innovations available at no cost. If innovations are given away and/or IPR is not enforced can private industry survive? Can new companies obtain funding if innovations are unprotected? Creative management of IP for humanitarian purposes is urgently required.

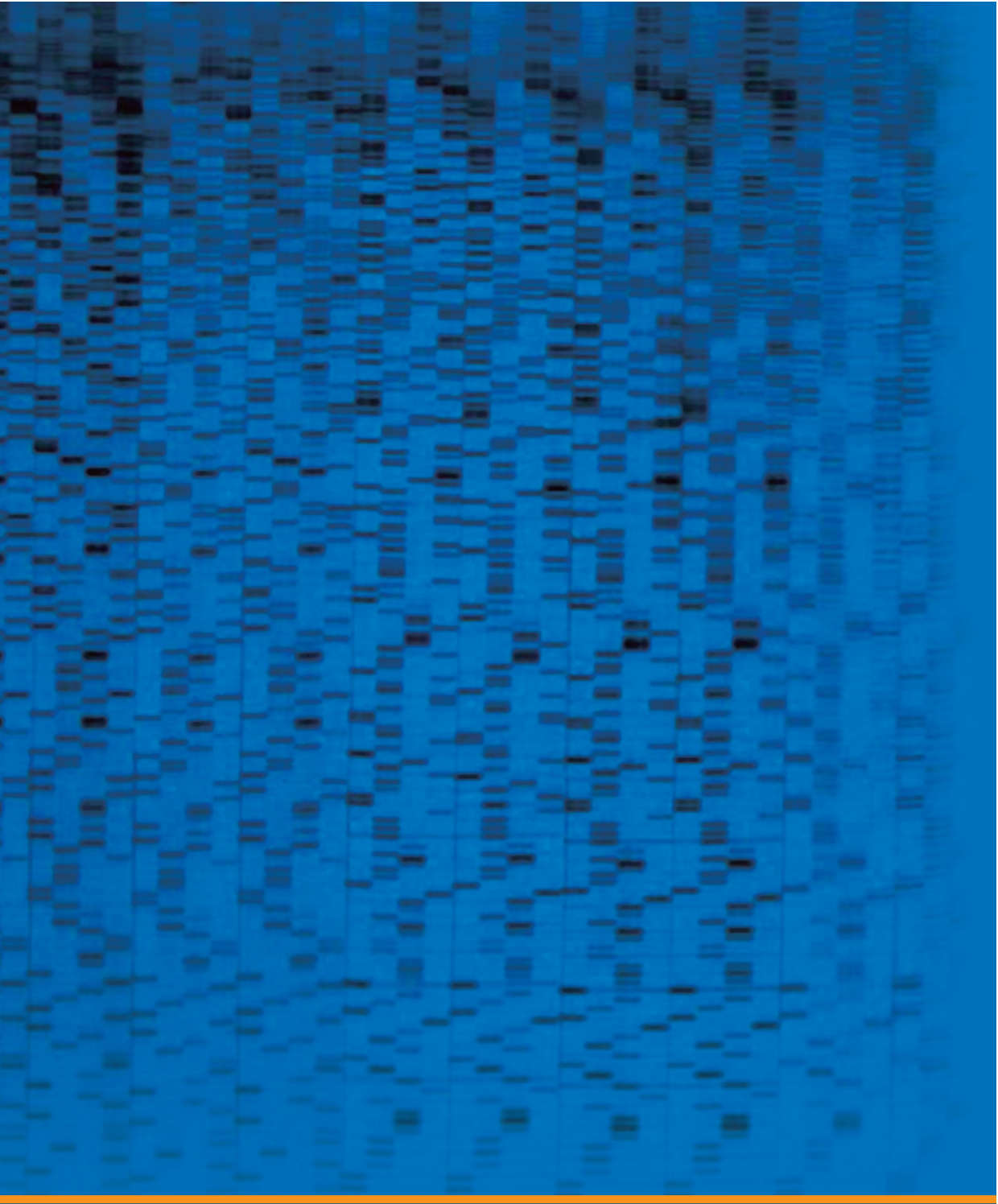
Another concern is the "freedom to operate" when conducting biotechnology research. Generally, the researcher and the researcher's organization want the right to use their innovations for commercial purposes, or they might want to freely share these innovations with other researchers and/or be able to allow anyone to use them.

However, in biotechnology research the researcher often uses materials and information developed by others. These others, the owners of these materials, may allow other scientists to use the materials for research purposes only. The owners contractually forbid the research user to do more than conduct research with their materials, and will not allow the researcher to commercialize new innovations or share them with others. Hence, they prevent free exchange of information and/or materials and they greatly impede the researcher's freedom to operate. How can this problem be managed? Should the "give away" philosophy be used to overcome this problem? Should scientists do research for the joy of it and just let companies innovate for the benefit of humanity? Will companies work to solve problems without an economic reward? This is not just a problem in industrial countries, but is a universal problem and needs to be fully addressed so scientists will have the freedom to operate.

Conclusions and Recommendations

- In the Trade, Patents, and Developing Countries arena there are many questions that need to be answered before developing countries can build viable and vigorous biotechnological programs that will benefit their society. Interestingly enough, many of these same questions need to be addressed by industrial countries.
- Ethical considerations are important in all intellectual property and IPR interactions between the North and South, the South and South, and North and North. No one country should impose its ethics on another.
- Building biotechnology capabilities does more than just provide innovations. In particular, it helps build human dignity.
- The development of new companies based on biotechnological innovations is difficult, but the development of these companies in developing countries will be most difficult. Considerable governmental assistance may be needed to build companies based on research results.
- Biotechnology products have proven over the past 30 years to be extremely safe. Misconceptions are most damaging to the acceptance of biotechnological products. A vigorous and continuing education program on the safety of such products must be undertaken to overcome the many years of misleading statements and assumptions.
- Capability constraints may be more of a problem in biotechnology research in developing countries than limitations posed by availability of intellectual property. Biosafety laws, enforcement of these laws, and building research capacity are all needed to build an active and effective biotechnology research program.
- South-North interactions in biotechnological research should be proactive, not reactive. It is essential for everyone to work together and to look forward to developing a means for all to carry on meaningful and productive research.

- South-North parties must work together through biotechnology to build the world's capability to better care for all people.
- Solving world IP/IPR biotechnology problems will require thinking and working outside the traditional IP "box." This will require the world to meet the challenge posed by Ismail Serageldin: "Dare to Dream, Be Bold."



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