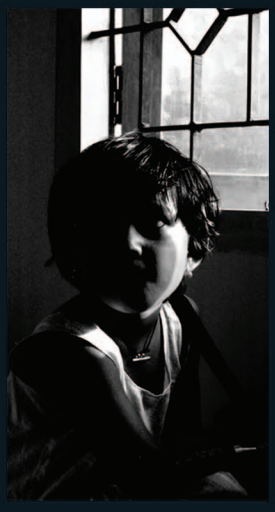
Changing Lives



BioVision Alexandria 2006

Ismail Serageldin | Ehsan Masood

with

Mohamed El-Faham | Amani Massoud

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Preface

Infectious diseases, cancer, diabetes, diseases of poverty and malnutrition: The healthcare and food security challenges facing us all today can at times seem overwhelming. Indeed, in many countries and for many people, they are the cause of much loss of life and incalculable suffering.

When it comes to diseases such as malaria, diarrhoea-and-dysentery, and tuberculosis, the poorest among us are more likely to be susceptible. Moreover, they are doubly hit. First, because they are more likely to live in countries where they remain outside the reach of public healthcare systems. Second, being on low incomes means they have no way of paying for private treatment.

At the same time, some diseases, such as diabetes and cancers are indiscriminate in who they target. These diseases are a function of the fact that (in both developed and developing countries) we live longer, we lead more indoor, sedentary lives; we smoke and we consume a range of foods that, even one generation ago, were alien to many.

One of the aims of BioVision Alexandria 2006 was to highlight both the challenges and the successes in delivering better healthcare and nutrition to those most in need; but also to demonstrate the potential that the new life sciences offer for enhanced nutrition, food security, environmental sustainability and universal and affordable healthcare for all.

BioVision Alexandria 2006 was well-placed to undertake this task. Indeed, it was a rare gathering, because leading scientists, policymakers, members of the business community, active members of civil society, citizens from both developed and developing countries came together in a spirit of partnership, and as equals, to talk about resolving some of the major challenges of our times.

BioVision Alexandria is always a major public event in its city's calendar. The 2006 event was no exception. Nearly 1600 participants came from all over Egypt to take part in Changing Lives. Among them – indeed, the vast majority – were students and teachers from schools, colleges and

universities. Most came at their own expense to learn, and to contribute to the discussions. It was a remarkable sight and a memorable one too.

The delegates included people who will have returned home inspired to take up careers in R&D, in policy, business, or to become more engaged citizens. We need all of these, and in far greater numbers because tomorrow's challenges will be even more complex and more urgent than those of today.

Jean-Marie Lehn, Nobel prizewinner in chemistry in 1987, said that a better world for us all is an achievable aim, and is not some faraway dream. For four days in April 2006 BioVision Alexandria showed – in a very small way – what such a world might look like.

Ismail Serageldin
Ehsan Masood
Editors

Acknowledgments

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Last, but by no means least, very sincere thanks to our partners BioVision Lyon who inspired us to take this road. We hope to meet again in Lyon in 2007.

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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
CAGE	Cap Analysis of Gene Expression
CBD	Convention on Biological Diversity
CGIAR	Consultative Group on International Agricultural Research
CJD	Creutzfeldt-Jakob Disease
CIBCM	Centro de Investigacion en Biologia Celular y Molecular
CLIMA	Centre for Legumes in Mediterranean Agriculture (Australia)
CNS	Central nervous system
CPGGH	Canadian Programme on Genomics and Global Health
CPVO	Community Plant Variety Office
CWANA	Central and West Asia and North Africa
DCPP	Disease Control Priorities Project
DArT	Diversity Arrays Technology
ECF	East Coast Fever
EST	Expressed sequence tags
FANTOM	Functional Annotation of Mouse
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration (US)
GAVI	Global Alliance on Vaccines and Immunization
GCGH	Grand Challenges in Global Health
GEF	Global Environment Facility
GIS	Geographic information systems
GOAL	General Optical Allocation of Land-Use
GMHT	Genetically modified herbicide-tolerant
GPS	Global Positioning System (of satellites)
GURTs	Genetic use restriction technologies
IAMP	Inter-Academy Medical Panel
IAP	Inter-Academy Panel

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
ILRI	International Livestock Research Institute
IPGRI	International Plant Genetic Resources Institute
IPR	Intellectual property rights
IRRI	International Rice Research Institute
IWMI	International Water Management Institute
JIT	Just-in-Time
KHCC	King Hussein Cancer Centre
LMIC	Low and Middle Income Countries
MAS	Marker-assisted selection
MECC	Middle East Cancer Consortium
MHLW	Ministry of Health, Labor and Welfare (Japan)
MSI	Millennium Science Initiative
MTA	Material transfer agreement
NARS	National agricultural research systems
NCI	National Cancer Institute (US)
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	The Institute for Genome Research

TILLING	Targeting Induced Local Lesions In Genomes
TRIPs	Trade-Related Aspects of Intellectual Property Rights
TWAS	Academy of Sciences for the Developing World
TWNSO	Third World Network of Scientific Organizations
TWOWS	Third World Organization for Women in Science
UNCCD	United Nations Convention to Combat Desertification
UNCED	United Nations Conference on Environment and Development
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 Organization
UPOV	International Union for the Protection of New Varieties of Plants
URES	Urban Rural Epidemiology Study (Chennai)
WANA	West Asia and North Africa
WHO	World Health Organization
WIPO	World Intellectual Property Organization

BioVision Alexandria 2006: An Overview

Rafik Nakhla and Amani Massoud

Challenges

Infectious diseases are among the biggest killers in developing countries. On the conference's opening day Peter Doherty, winner of the 1996 Nobel prize for medicine, reminded us that some 30 new diseases have been discovered in the past three decades. Many of these (such as HIV/AIDS, SARS and avian influenza) have transferred from animals to humans, and are a direct result of several factors that have come together at the same time: population growth, the fact that many more people travel than in the past, and the consequent increase in contact between humans and animals.

Yet at the same time the burden from non-communicable diseases is no less severe. BioVision 2006 chose to highlight two examples: diabetes and cancer. Boerge Diderichsen said that in 2007, some 230 million people worldwide will have diabetes. Of these, some 3.5 million will die because of this disease. Diabetes is sometimes mistakenly seen as a developed-world illness. But the progressive urbanization of the developing world, coupled to changes in diets and more sedentary lifestyles has seen diabetes rates increase across the developing world. According to Samir Assaad Khalil, Egypt will have the largest number of diabetes sufferers in the Middle East/North Africa region by 2025. Some surveys report diabetes incidence at one in ten of the adult population in Egypt's urban areas, rising to one in five among the wealthiest populations. The lowest rates of

diabetes, in contrast, are in rural desert areas. In parts of India, according to Vishwanathan Mohan, rates are as high as 20 per cent for all adults.

Along with diabetes, cancer rates have also taken an upturn in the developing world. The most important variable that unites the majority of the world's cancer sufferers, Joe Harford told the conference, is age: nearly half of those diagnosed with the disease are aged 65 or over. In the Middle East, life expectancy is increasing. Harford said that out of all of the world's regions taken together, incidence of (and deaths from) cancer in the Middle East will be among the highest in the world. Each year there are some seven million new cases of cancer worldwide. Deaths from cancer, currently at 11 million, will rise to 16 million by 2020: 70 per cent of these deaths will occur in the developing world.

A Role for Life Sciences

The fight against disease and malnutrition can be won and in a number of cases, steady progress is being made, none more so than in the crucial area of diagnostics. The Disease Control Priorities Project, which was launched at BioVision Alexandria, is perhaps the most comprehensive diagnosis that we now have of the world's healthcare priorities, and how to meet them.

Take diabetes. According to Boerge Diderichsen, one of the principal factors in diabetes deaths in developing countries is that a diagnosis is made too late to save lives. Education and public awareness, says Diderichsen, remains what he calls "the heart and soul" of diabetes care. Public awareness is also an important factor in helping to get vaccines to the 27 million newborns and 40 million pregnant mothers who are not getting immunized, says Stephen Jarrett; and, according to Ysbrand Poortman, in helping to reduce the global incidence of congenital and genetic disorders at birth.

While public awareness of health and nutrition is key to better health, accurate diagnosis cannot be made without R&D. And it is in R&D that new developments in the life sciences are all set to take disease diagnosis to a whole new level. Abdallah Daar, Peter Singer and colleagues, for example, demonstrated to the conference the potential of genomics in

developing diagnostic testing kits, as well as in vaccines production and in drugs delivery.

In addition to healthcare, it is food and nutrition where new life sciences are, quite literally, changing lives. At present, the major biotechnology developments taking place in agriculture are in a few commercially-important crops. But the scale of application and adoption is important. Clive James' annual assessment of global agricultural biotechnology shows the rapid adoption by governments and by farmers of genetically-modified crops. Some eight million farmers now grow seeds that have been produced using gene technologies over an area of some 200 million acres in 21 countries. A handful of mostly export-bound crops developed in the private sector dominate the commercial-scale use of agricultural biotechnologies. But delegates at BioVision 2006 saw a glimpse of scale and ambition that biotechnologies could hold in world agriculture.

Take the eggplant, for example. This is one of Asia's most important vegetables. It is also vulnerable to one particular pest, which has on occasion resulted in the destruction of 90 per cent of an eggplant crop. To control this pest, Frank Shotkoski said, farmers need to spray an insecticide as often as three times per week. This threatens not only their own health, but also the health of consumers and the environment. The best possible solution to this is likely to be an eggplant seed that is already in production and which has been modified with a gene to resist the borer.

New gene technologies are also being investigated to be able to help plants to grow in drought-like conditions; which can fortify crops with important vitamins and minerals, and which can increase the yields of staple crops, such as rice. According to Gurdev Khush, farmers will need to produce 40 per cent more rice by 2030 if they are to keep up with demand in Asia, where more than 90 per cent of rice is grown and consumed.

Protecting People and the Environment

There exist some 200 million acres of GM crops that have been approved by regulators. But an equal quantity (200 million acres) has been planted worldwide without regulatory approval. These crops officially do not exist, which will make it harder to take appropriate action in the case of potential accidents or from environmental risks.

New technologies are being developed at a rate that is unsurpassed in human history. Public and environmental safety makes it all the more important for regulation to keep pace with development in what Calestous Juma and Ismail Serageldin are calling the 'co-evolutionary' approach.

Green revolution technologies helped to secure food security for hundreds of millions of some of the poorest people in Asia and Latin America. But we now know that this revolution was not cost-free. Land-degradation has been one of its known impacts; a second is the cost to human health experienced by those who come into regular contact with chemical pesticides. The challenge for the new life sciences, according to M. S, Swaminathan is to achieve an 'evergreen revolution', in which the gains from agricultural technologies can be achieved with minimum or no human or environmental costs.

1

FIRST WORDS

1

Changing Lives With the Life Sciences

Philippe Desmarescaux

The Life Sciences will without doubt be the key to many of the major issues of the 21st century. This is confirmed, on a daily basis, by news stories from all the continents – and even from the oceans, as the following examples show:

- The contribution of life sciences in health, nutrition, agriculture and environment is evident.
- Given the finite nature of our natural resources; water, soil and oil, the life sciences will offer us a new view on the three Rs: Reduce, Re-use and Re-cycle.
- Enzyme catalysts and biological processes derived from living cells should allow us to reconfigure industrial processes, in areas as diverse as industrial chemistry and informatics. Such processes will become more efficient, more reliable and consequently more cost-effective - with less impact on our environment.
- Life sciences will contribute also greatly to improve our personal safety and security, which will become a priority for all of us.

Looking at modern trends, no one can ignore the impact of the life sciences. However, if we share this view, we have not yet done enough to support the very real possibilities offered by the life sciences.

The following issues are crucial:

- In all nations, basic research generating new knowledge, new concepts and new approaches to problems should endeavour to tackle these issues. Such new knowledge should be accessible to all. All countries must rely on their own university-based research teams so that we can call upon – and count upon – the solidarity of the global scientific community and the richness of its cultural diversity. This resource will reliably communicate the hopes, difficulties and potential risks of the life sciences. Some countries cannot support the cost of such fundamental research and we must all count upon international solidarity, at the level of individual nations, international organizations and private foundations. Such solidarity will allow those countries to realise the potential of bright minds that might not otherwise be recognized.
- The spread of knowledge will allow more and more citizens to understand and accept the necessity of advances in life sciences, linking such advances to careful but positive progress. Global society can no longer accept the consequences of ignorance, such as the rejection of vaccination in some nations, or the rejection of GMOs (genetically modified organisms). Such ignorance is an unacceptable brake on progress that will slow-down or compromise advances made possible by research in the life sciences, and expose us all to danger.
- These efforts in education and popularization are difficult, especially in an area of science that seems so complex – and which changes so fast. For all of us, however, this effort must be considered as one of our most burning ambitions. Together we can succeed in this mission, but only if each nation can count upon the availability of internationally-recognized universities and the brightest minds.
- It will also be important, if we are to avoid precipitate actions, to establish an ethical and regulatory framework. This will take into account, and manage, any secondary effects of new knowledge and its implementation, applying intelligently the Precautionary Principle. This ethical and regulatory framework will also comfort public opinion, fellow citizens, that progress, while never being without risk, can be responsibly managed by concerned scientists and industrialists. As knowledge progresses so will the corresponding ethical and regulatory apparatus. It goes without saying that the ethical and regulatory

framework must be coherent and consistent from nation to nation, so as to offer science and industry a secure framework for progress that transcends international frontiers.

To meet all these challenges it will be necessary to establish broad and multi-dimensional cooperation:

In Science; with a multi-disciplinary approach linking the 'hard' sciences, chemistry, physics and biology; as well as the social sciences, sociology, philosophy, anthropology etc., that might offer a conceptual and social framework for successful progress.

In industrial and economic exploitation; by integrating traditional activities with the new technologies.

Geopolitically; by including nations from the developed North as well as the developing South.

Socio-politically; with the coming together of political representatives of nations, international organizations and NGOs (non-government organizations) – to include those representing both the North and the South.

Going beyond dialogue, real partnerships must emerge, bringing together qualified representatives from these communities.

We cannot hope to save the world in four days. However, thanks to the meetings organized alternately in Lyon and Alexandria in the framework of the BioVision Forums, we can hope, through our dialogue, to make gradual steps towards a common vision and some common action.

2

New Directions for Science Policy in Japan

Koji Omi

Science and technology is essential for sustainable growth and for the betterment of the global community. Based on this awareness in Japan the Science and Technology Fundamental Law was enacted in 1995 and I personally devoted myself, with my colleagues, to ensuring the passage of that law in the Diet. Under the Fundamental Law, a five-year national strategy, the Science and Technology Basic Plan was formulated. The first and second terms have ended, and the third term Basic Plan has just begun.

One of the features of the Basic Plan is to boost the national R&D budget for the next five years. In the first five-year plan, we devoted some $150 billion, a 40 per cent increase from the previous five years. In the second plan, we increase this further to $190 billion. Under the third Basic Plan, we have set a target budget of 25 trillion yen, which is equivalent to $230 billion.

In the Basic Plan, life-sciences are regarded as one of four strategically important areas, along with information technology, nanotechnology, and environmental sciences.

Since the deciphering of DNA by Watson and Crick, biotechnology has progressed at unimaginable speeds. In particular, the impact of sequencing

the human genome has been substantial, leading to growth in life sciences research and opening the door to the post-genome era.

But at the same time, these discoveries amount to little more than a mere glimpse of the complex mechanisms of life. For example, some of the non-coding genes that we previously used to call Junk DNA have turned out to be functional RNA. This should not come as a surprise as there is nothing that exists in nature that is devoid of value or purpose.

Now that we have discovered many of the component parts on which life's complex mechanisms are based, future research should be directed to discovering how those parts are integrated to function to make life as we know it. In Japan, an important direction in our life sciences strategy is to promote those disciplines that can help us to understand life as a system. Foremost among these is the field of what is called systems biology, which attempts to combine our understanding of individual components to understand the complex mechanisms of life.

So much for basic sciences, in more applied fields, genome-sequencing data is being put to good use in developing new medicines. For instance, research in what are called Single Nucleotide Polymorphisms (SNPs) provides glimpses of a future in which medicines could be produced to suit individual medical needs. Similarly, research in the field of proteomics has the potential to enable us to detect cancer earlier than before. New technologies in drug-delivery systems will allow us to use drugs with more efficacy and fewer side-effects. Equally important is what we call 'translational research', which helps to deliver the results of research from bench-to-bedside.

Life sciences as we all know also include issues that are beyond the control of any single country and that need the consensus of a range of people: policymakers, business leaders, scientists, opinion formers and all citizens. In Japan, we host a regular Science and Technology in Society Forum, which we believe is an important mechanism for discussing what I would call the 'lights and the shadows' that are cast from life sciences.

3

Connecting the Disconnected

Elias Zerhouni

Globalization is happening. But it doesn't mean the same things to those who are being affected by it. What do I mean when I say this? Globalization for many means remarkable progress and many benefits. For some three billion, for example, it means better infrastructure, the ability to communicate in an instant, to be able to travel great distances in a matter of hours; and the benefits that are to be had from being a part of an integrated global economy. But globalization for another three billion means something else: these are the people who are disconnected, who are not a part of the global economy, and for whom knowledge-per-capita, and access to public health is decreasing.

What does this mean from the standpoint of the US National Institutes of Health? First, it is important that we retain a global perspective when looking at globalization: that we take into account the perspectives of both: of those who are connected, but also those who are not. These are not geographic divisions: there are many that are disconnected in the midst of a connected world, such as the United States. At the same time, there are many who are connected to globalization in countries such as China or India. Second, our institutions need to be prepared and equipped to address issues raised by globalization, institutions such as the Fogarty

International Center. They also need to be funded -- over the past 4 years we have tripled our commitment to global science.

We believe that over the next 25-to-30 years, there is going to be an acceleration of discoveries in science. It is imperative, therefore, that we build an infrastructure, a connected infrastructure, and one that can increase knowledge-per-capita; increase the quantity of information that is transferred to those who do not have it; and increase the numbers participating in the global economy.

The challenge that we all must overcome is to connect the disconnected.

4

Global Institutions with a Southern Flair

Mohamed H. A. Hassan

TWAS served as a co-sponsor of BioVision Alexandria 2004 and were proud to do so again in 2006. This biennial event not only highlights the growing international reputation and prestige of this magnificent institution, Bibliotheca Alexandrina, but also reflects a welcome trend in North-South cooperation in the life sciences – a global partnership that promises to provide substantial benefits to our increasingly global society. I am particularly encouraged by the contribution that this partnership could make towards advancing the Millennium Development Goals, the cornerstone of international efforts to reduce poverty, hunger and disease in the world's poorest places.

In December 2005, Bibliotheca Alexandrina, under the leadership of Ismail Serageldin, hosted TWAS's 16th General Meeting, which was opened by the President of Egypt, Hosni Mubarak, and attended by more than 250 internationally renowned scientists, scholars and policy makers, mostly from the developing world.

During that meeting, participants discussed, among other things, issues related to the building of centres of scientific excellence; the nurturing of a new generation of talented scientists and technologists; and the promotion of women in science. These are all critical issues, especially in developing countries. Our 16th General Meeting in Alexandria also recognized the

importance of the social sciences, especially when addressing issues related to harnessing science and technology for sustainable development. I might add that strengthening the ties between the natural and social sciences has been a central aspect of the mission of the new Bibliotheca Alexandrina, which is serving as worthy successor to the ancient library of Alexandria, antiquity's most noteworthy sanctuary for scholarship and science.

TWAS is a merit-based academy of sciences whose membership includes more than 800 eminent scientists. Its unique status stems from its international membership, representing more than 90 countries, and from the fact that more than 80 per cent of our members live and work in the developing world. Indeed, we like to think of ourselves as a global institution with a southern flair.

Our uniqueness is also derived from the fact that TWAS now serves as the umbrella for several other institutions that share the same goals, including the Third World Network of Scientific Organizations (TWNSO), the Third World Organization for Women in Science (TWOWS), the Inter-Academy Panel on International Issues (IAP) and the Inter-Academy Medical Panel (IAMP). Together, these institutions and their regional offices represent a formidable source of expertise and global action on matters of science and science policy worldwide – and especially in the developing world. Some of our activities include:

Plans for a Regional Young Scientists Conference in the life sciences that will be held in conjunction with the next TWAS event. About 50 talented scientists under the age of 40, selected through a rigorous competitive process, will participate in the conference and then attend the TWAS general meeting.

The Third World Organization of Women in Science (TWOWS), held its Third General Assembly in Bangalore in November 2005. More than 200 women scientists not only celebrated their progress over the past several years but also discussed the challenges that lie ahead. Women scientists are now the majority in many university classrooms, most notably in the fields of biological, medical and environmental sciences. In the State of Qatar, for example, 75 per cent of all university students are women. Whether this new generation of talented women scientists will move up the professional ladder to professorships, rectorships, university presidents and ministers, in the same numbers, remains to be seen.

The InterAcademy Medical Panel (IAMP) held its Second General Assembly in Beijing in March 2006. The highlight of the meeting was the launch of the reports of the Disease Control Priorities Project (DCPP), a collaborative effort of the Fogarty International Center of the US National Institutes of Health, the World Health Organization and the World Bank, with funding from the Gates Foundation. These reports provide a detailed roadmap for improving public health in the developing world. In Beijing, IAMP also outlined its future programmes that include the expansion of its mother-and-child research network and that call for research activities to examine such critical issues as perinatal mortality, rheumatic fever and quality care in hospitals. With the knowledge and expertise prevalent among its members, I am confident that IAMP can make significant contributions to all of these issues.

The InterAcademy Panel (IAP) held its Third General Conference at Bibliotheca Alexandrina in December 2006, thanks largely to a generous invitation from Ismail Serageldin. Presidents and representatives of over 90 merit-based science academies worldwide attended this IAP Conference to discuss issues related to the promotion of basic sciences for sustainable development and the increasingly important role of academies in providing evidence-based and credible advice to decision-makers on scientific issues of critical importance.

TWAS and its partner organizations stand ready to contribute to the goals and follow-up activities of BioVision Alexandria 2006 conference. The central themes of this conference – food security, environmental well-being and ethics – are critical to scientific communities and, more generally, to societies across the globe.

One of the main tracts focuses on drought. TWAS and the Third World Network of Scientific Organizations (TWNSO), in cooperation with Harvard University Press, have published a beautifully illustrated book entitled *Dry: Life Without Water*, describing how people living in arid and semi-arid regions have learned to cope – and, in many instances, thrive – in environments where water supplies are scarce and often unreliable. Their stories offer lessons of hope and determination that we, as scientists, scholars and citizens, can all learn from, as we seek, together, to create a better world.

The title of this volume, *Changing Lives* is indeed an apt one. I would only add that we are living in an era where not only the life sciences but

all sciences are facing new opportunities and new challenges that promise to change all of our lives in ways that we can barely imagine. Think of the promise of nanotechnology to produce cheap and effective water-filtering systems or to develop innovative methods of diagnosing and treating diseases. Last year, for example, Chinese scientists created a protein nanochip capable of detecting hepatitis B and C.

Its a major responsibility of the scientific community – both in the developing and the developed world – to help ensure that the changes that do take place are for the better, and that we serve not only our colleagues and professions but our societies. This is a role that scientists may not be accustomed to, but it is a role that they are obliged to play as science gains an ever-more central place in our global village.

5

A Quantum Leap for Science and Technology in Egypt

Hany Helal

Minister of Higher Education, Egypt

The Bibliotheca Alexandrina was not just the venue for BioVision Alexandria 2006. It is also a leading centre of excellence for the production and dissemination of knowledge.

I was one of the UNESCO officers tasked with following-up on the construction of the library in the 1990s once the decision had been made to take this project forward. I remember thinking at the time whether this wonderful building would become an active library, or whether it would become yet another 'white elephant'. BioVision Alexandria 2006 and much more is a witness to the fact that this library has out-performed even the most optimistic expectations of what it was intended to achieve.

BioVision represents a unique opportunity for people from both developing and developed nations to discuss science and the finest achievements of the human intellect, to exchange knowledge, information, innovation and new ideas, and to encourage constructive dialogue between key players to better meet the challenges that we face in our new century. Life science is the most compelling science of our times. It holds great promise in helping to tackle hunger, provide better healthcare, and protect the environment.

Our President Hosni Mubarak has clearly indicated that education, science and technology are top priorities for Egypt. The development of an indigenous capacity in science & technology is an absolute necessity for the sustainable development of Egypt.

In Egypt, we are in the process of thinking hard about how to give our science and technology a major boost. The main features of any future policy will include: developing human resources with a special focus on building the capacity of younger generations; improving our research institutions; promoting public-private partnerships and looking at new ways to finance R&D.

We plan to achieve our goals through cooperation and networking; by working closely with world-class institutions; focusing on our newer generations, but at the same time benefiting from our more experienced experts; making the best use of our resources and providing clear leadership.

6

International Research Cooperation is Key to Sustainable Development

Janez Potočnik

Modern life sciences and biotechnology are likely to be among the next generation of engines for economic development in both industrialized countries and in emerging economies. So much so that many of these countries have already placed the life sciences (and biotechnology in particular) at the forefront of their national research agendas. At the same time, advances in the life sciences have the potential to provide opportunities for enhancing sustainable development, particularly among our poorest populations. Europe can and will play a vital role in advancing this agenda. We have no choice, for our own wellbeing, but also for the wellbeing of our planet. The European Union is committed to contributing in a substantial way to the global fight against hunger, against disease and against extreme poverty.

European cooperation with developing countries in the fields of science, technology and development has a long, proud and a deepening history. In recent years alone -- between 1998 and 2002 -- for example, the European Commission funded hundreds of research projects worth hundreds of millions of Euros with developing countries. Opportunities for such collaborative research have increased further since 2002. This collaboration is particularly strong in the field of healthcare research. We

have set aside a budget of 200 million Euros towards the development of medicines and vaccines against HIV/AIDS, malaria and tuberculosis

The role of the scientific community in this regard is particularly crucial. And I am pleased to recognize the role being played by a group of prominent researchers from both developed and developing countries in setting up the EAGLES forum -- European Action on Global Life Sciences. This forum encourages debate and discussion at the highest levels on realizing the needs of the least developed countries, and it seeks solutions from those involved in both research and policy. It is only by joining forces that we will move mountains. But at the same time, we also need to be realistic: the answers to the questions that we seek will not come about overnight. This will be a long process.

The European Union is committed to continue playing our part in addressing these challenges. We will, in addition, contribute to the United Nations Millennium Development Goals for eliminating extreme poverty and hunger, and ensuring environmental sustainability before 2015 through a dedicated package of research in health, food, agriculture and the environment.

It is my considered view that the quality of life in both industrialized and developing countries are inextricably linked. We are on this journey together, and this is why international cooperation in science and technology towards sustainable development is so crucial. Sustainability and global competitiveness are not mutually exclusive. They must go hand-in-hand for the prosperous and sustainable future of our common planet Earth.

2

NOBEL LAUREATES: IDEAS, PERCEPTIONS AND INSIGHTS

7

A Century of Nobel Prizes

Erling Norrby

Alfred Nobel received the first of his 355 patents in 1863 – it was for the use of nitroglycerin as an explosive, in dynamite. A year before he died, Nobel wrote his now famous final will: the creation of an endowment that would award cash prizes worth $ one million for excellence in physics, chemistry, physiology or medicine, literature and peace. His concept was a simple one: the science and medicine prizes were to be given to talented younger scientists enabling them to concentrate on their work without the need for an income for some 20 years.

The practice has been somewhat different: the science and medicine prizes have been awarded to more mature researchers, and has given them global visibility as a result. The first three prizes are given for a single discovery that has significant impact – rather than recognizing a lifetime's contribution to science. Another departure from the original will is in the fact that prizes are not given out for work that would have been carried out in the year preceding the award. In practice, scientific discoveries have been recognized up to two decades after they were first reported. One recipient, Peyton Rous, had to wait half a century before his discovery of tumour-inducing viruses was recognized in 1966.

The prize awarding institutions are: The Royal Swedish Academy of Sciences (in physics and chemistry); The Karolinska Institute in Stockholm (for physiology or medicine); The Academy of Letters in Stockholm (for the literature prize). The peace prize is given by a five-member committee appointed by Norway's House of Parliament, the Stortinget.

The Nobel Foundation was soon established to coordinate the management of the fund and to arrange for the annual prize-giving ceremony that takes place in Stockholm on 10 December, the anniversary of Alfred Nobel's death in 1896.

A single prize can be shared between no more than three recipients – even though this was not in the original will. A single individual can, however, receive more than one prize as was the case with John Bardeen who received the physics prize in 1956 and again in 1972, or Frederick Sanger, who received the chemistry prize in 1958 and again in 1980.

Individuals can also receive honours in different fields, such as Marie Curie's physics prize in 1903, and her chemistry prize that was awarded in 1911. Similarly, Linus Pauling was awarded the chemistry prize in 1954, and the peace prize eight years later in 1962. Nobel prizes are also frequently awarded to institutions. The Red Cross, for example, has been given the peace prize on three occasions.

The process for selecting the prize-winners is (and has to remain) a secret. This is a prerequisite, and is designed to help endow the process with as high degree of objectivity as is possible in human endeavours. Without knowledge of the process, lobbying becomes useless, indeed, can have a negative effect.

By 2005, some 510 people had received prizes in the science fields. Recipients from Germany predominated up to the Second World War. In the 50 years since, more than two-thirds of recipients in the natural sciences have been from the United States.

What would Nobel have thought had he been alive today? He would likely have been very surprised. His intention in the will was to reward contributions from talented younger scientists that were "beneficial for mankind". The Nobel committees have interpreted this by awarding prizes to high quality basic research that leads to discoveries, which (even if much later) help to advance our civilization in some way.

8

A Life in Physics

Georges Charpak

(Physics, 1992)

I am a scientist with the good fortune of having straddled two centuries, both of which are characterized by inventors and inventions. Most of my work was in the last century – one of major discoveries such as radioactivity and the structure of matter. This was also the century of genius, such as the genius of Albert Einstein.

At the age of seven, I found myself in France having arrived from Poland. Physics was my passion and I later began to work in the Joliot-Curie laboratory in Paris. I quickly discovered my strengths. I couldn't make things work, but had this ability to understand why things work as they do (or as they didn't). It was clear to me then that my destiny as a scientist lay in becoming an experimentalist, and I became an 'image hunter'.

Images are fundamental to physics, as they are to many, if not most scientific disciplines. An accurate reproduction of an image is even more so. In the 1950s, a new generation of particle accelerators were coming into use, such as the underground circular-shaped laboratory at CERN on the border that divides France and Switzerland. These colliders would in time lead to the discovery of new particles. But the discovery of these particles would require the development of new and accurate detectors. New detectors are what I would dream about while doing my PhD and beyond.

Devices that can detect fundamental particles have applications that extend beyond experimental physics. They are used in the pharmaceutical industry, for example, as well as in radiology: they can help to visualize the reconstruction of a bone in three-dimensions, for example.

Today, research in science and technology in my own field and in others is progressing at speeds perhaps greater than at any other time in history. We should be concerned, particularly at the explosion of information, but also at the lack of education among so many people, and our continued destruction of the environment.

Education and solidarity are the two keys to a better future.

9

The Millennium Science Initiative

Harold Varmus

(Medicine, 1989)

Science helps to feed the hungry, heal the sick, protect the environment and it can also provide dignity in work and create space for the joy of self-expression. Science, however, is not accessible to many in the world's poorest countries. This puts an imperative on the scientific community to make science more accessible and hence a global activity. The main focus of our work needs to be to make information more accessible – to make scientific publications freely accessible.

Making science a global activity has four components to it:

- Creating high quality research facilities
- Fostering meaningful exchange
- Focusing attention on crucial topics
- Making information accessible

The Millennium Science Initiative (MSI) began in 1999 as a joint activity of the Science Initiative group at Princeton University and the World Bank. The aim was to support centres of excellence in low-income countries with an initial focus on Chile and Brazil, and later including Mali and Uganda. MSI has so far awarded 43 grants worth a total of $430 million for teams from developed and developing countries.

MSI also seeks to encourage scientists from developed countries to engage positively, promote personal exchange, and engage in sabbatical visits to MSI centres in poor countries. The Mali Malaria Research and Training Centre is an example of one such centre of excellence.

Making information more accessible can happen through two approaches:

- Public digital libraries such as Pub Med Central at the US National Institutes of Health; and the DNA sequencing data that is being stored in the public database Genbank.
- Open Access publishing, for example through the Public Library of Science (PLOS) and Bio Med Central, based in London.

PLOS was created as a non-profit alternative to conventional scientific publishers which are profit-making companies and charge large amounts of money for providing access to scientific information. The principle behind PLOS is that scientific information, which has already been paid for in the form of a public subsidy, should be available to citizens free of cost.

10

Plagues, Pestilence and Influenza: The Role of Infection in Human History

Peter Doherty

(Medicine, 1996)

One hundred years: that is the length of time for major advances in our understanding of infectious diseases. Before then, infectious diseases such as plague caused much death and destruction. In the 14th century, for example, plague wiped out as much as 50 per cent of the populations in the cities of Europe.

One of the areas in which our understanding is significantly better than in the past is how diseases transmit from animals to humans. Since 1979, some 30 such new diseases have been discovered. They include Ebola, Sars, HIV/AIDS and Influenza.

Take Ebola: this fever is an infectious disease that is believed to be maintained in an as-yet unidentified forest dwelling-species mainly in central Africa. The bad news is that mortality rates from Ebola infections are as high as 90 per cent. Better news is that an effective vaccine now looks to be within reach.

The disease that preceded AIDS was discovered by Beatrice Hahn at the University of Alabama in the US, by sampling the faeces and urine of

chimpanzees. Unlike in humans, however, AIDS in chimps leads to only a mild infection.

The clinical features of Sars, detected in China's Guangdong province, were initially thought to resemble those of severe influenza. The most severe outbreak so far was in February 2003 when some 50 cases were being reported daily. The Chinese government's response was swift and they established a hospital for Sars cases in just eight days.

The Sars outbreak is an example of a potential pandemic that was kept under control. There was no such fortune with the influenza pandemic of 1917/18. This killed an estimated 40 million people. It took a further 15 years before the virus was successfully isolated. There were further influenza pandemics in 1957 and again in 1968. Influenza remains a potent threat. In the US alone it kills up to 35,000 people every year.

Thankfully, Avian Influenza has so far caused very limited human deaths, in part because the virus has failed to mix with a human strain, or mutate in such a way that it spreads easily between people.

We cannot, however, be complacent. One of the reasons for the increase in diseases that are spread between animals and humans is the rapid growth in the human family and the increased frequency of interactions between human populations and animals in the wild – such as in forests. Our rate of population growth is unsustainable.

11

A Better World for All: Dream or Reality?

Jean-Marie Lehn

(Chemistry, 1987)

Can science provide hope and a better world for all? I would say that this is a reality that is within our grasp: it is not a dream, nor can it be a figment of our imaginations. Moreover, the field of chemistry can play its part in achieving this end.

How? Chemistry is the science of how we understand and then transform living and non-living matter. You could say that it is the science of what I would call 'informed matter' – based on our ability to store information inside it. Self-organization plays a vital role in chemistry. This refers to how we describe, understand and create novel forms of complex matter, or thinking matter. It works by design as well as through selection.

Chemistry is vital for a better world through its role in the development of drugs. This is a direct result of the ability of research chemists to be able to synthesize naturally-occurring products, such as urea and vitamin B12.

Today, what we call molecular chemistry has given way to newer and more complex fields such as supra-molecular chemistry and combinatorial chemistry: chemistry that goes beyond the molecule, and that goes into systems, information and interactions.

Take combinatorial chemistry as an example. This is the synthesis of chemistry and information technology, and will be particularly important in the development of tomorrow's medicines. How does it work? Imagine a lock-and-key. The 'lock' represents a disease, and 'keys' are potential drugs. In traditional chemistry, much effort is expended in trying to fashion a single key to fit a lock. Combinatorial chemistry is a system in which researchers can try to fit a very large number of keys (drugs) into tackling a disease, using computer-modelling. One of these keys will inevitably turn out to be the correct one.

This is a chemistry that adapts to its environment. You could call it a Darwinian Chemistry. It is a part of the tree of knowledge, which will help us to shape our destiny.

This is my message of hope, and why I am confident that a better world is more than just an aspiration, but a practical and achievable reality.

12

Making Progress in Diseases of the Central Nervous System

Stanley Prusiner

(Medicine, 1997)

At some point in our lives, one in four of us will need to seek medical advice for a possible complaint of the central nervous system (CNS). This includes disorders such as Alzheimer's disease, or Parkinson's disease; schizophrenia or bipolar syndrome.

Despite the prevalence of such diseases, the quantity of new CNS drugs being produced is very small, especially if you compare them to drugs for cancers and cardiovascular diseases. The last significant new medicine for a CNS disorder was licensed more than four decades ago, for Parkinson's.

My own work is in a field known as prions. They are an altered form of protein and are implicated in the family of diseases known as Creutzfeldt-Jakob disease (CJD), which is the human form of Mad Cow Disease (Bovine Spongiform Encephalopathy). Unlike viruses or bacteria, prions lack DNA, or its messenger chemical, known as RNA. Prions come in different shapes and have varied incubation times: this is the time that elapses between when an organism becomes infected, and the development of the symptoms of a disease.

In the absence of new drugs to treat CNS diseases, what is of vital importance is that these diseases can be diagnosed and detected as early as possible. This is because, once symptoms become apparent, often very little can be done for a patient.

Science has much to offer people and the planet. It has achieved much in healthcare, nutrition and in improving quality of life. But there are some things that science cannot achieve: it cannot make all peoples behave in a rational way, for example. Similarly, there will always be politicians who will remain ignorant of science. Both of these must be improved if science is to fulfil its promise and potential of delivering hope to all of humanity.

3

SCIENCE AND THE HUMAN CONDITION

13

Health Discoveries in Perspective

Peter Lachmann

The enormous improvements in healthcare that have occurred in the last century-and-a-half stem from the development of rational medicine. Rational medicine is based, insofar as it is possible, on knowledge of physiological and pathological structure and function and is concerned with understanding disease processes and translating this understanding into improved healthcare, including the prophylaxis, diagnosis and treatment of disease. Inspite of the great successes of rational medicine, what I would call 'irrational medicine' still flourishes.

Irrational medicine has no basis in pathology and is frequently based on belief systems and encompasses universalist theories of the causation of treatment or of its disease. It rejects empirical evidence and therefore cannot learn from its mistakes. There are many diverse systems of irrational medicine of which I would like to mention just two.

The first is Galenical medicine stemming from the views of Galen in about 130 AD. He believed that disease was due to imbalance between four basic humours: the sanguine, the melancholic, the phlegmatic and the choleric. He taught that the balance could be restored by treatment with drugs or by procedures such as bleeding, cupping, purging and blistering, (all of which were unpleasant as well as potentially harmful). Galenical medicine survived as the orthodox system of western medicine for over 1500 years without any empirical evidence to underpin it; but it has now been almost universally abandoned.

When Samuel Hahnemann introduced homeopathy in 1810, there is no doubt that it was preferable to Galenical medicine. Homeopathy was based on what is called the 'Law of Likes' which states that drugs that produce a particular symptom at high doses will cure the same symptom at very low doses. There is no empirical or rational basis for this belief (although some have claimed to see in it an analogy with allergy and desensitization). However, homeopaths use such high dilution of their drugs that, in effect, they are giving only the diluent; and homeopathy clearly enough works entirely by placebo effect. Its great advantage in the early 19th century was that the treatment was harmless. It is, however, strange that despite the growth of modern pharmacology, homeopathy is still practised by large numbers of people who spend large sums of money on it. Although homeopathy remains a safer way of administering placebo than, for example, the use of non-steroidal anti-inflammatory agents, it is not harmless when used to treat diseases that require active treatment and the advocacy of homeopathic remedies in place of vaccination is most certainly extremely dangerous.

Keeping Healthy

It has become abundantly clear that our susceptibility to disease is not random. It depends on our genetic makeup; on our foetal and early life environment; and our immunological history (in which vaccination plays a large and important role). It also depends, to a large extent, on our lifestyle. It is known that tobacco smoking is a major cause of disease, as is excess consumption of alcohol and other addictive drugs. Sexual hygiene has always been of considerable importance and has become even more important with the advent of AIDS in the last quarter century. Diet is another important lifestyle factor, although here the evidence is sometimes more controversial. However, it is clear that both undernutrition and overnutrition are disadvantageous and that typical western diets carry risk factors both for heart disease and for certain cancers.

Some risk factors can be modified, blood pressure being one of the most important. Screening for raised blood pressure and its treatment at the asymptomatic stage is known to be a powerful preventative measure against stroke and heart disease. Similarly monitoring for blood sugar can

detect diabetes at a pre-symptomatic stage, and treatment can also reduce the risk of its complications.

Genetic Risk of Disease

It has long been known from family history studies that people themselves will know if many members of their family have been sick with the same disease. However, modern methods of genetic diagnosis enable genetic risk factors to be determined that may not otherwise be obvious, and this technology has attracted controversy.

One technique for avoiding serious monogenic disease is by testing prospective parents for the relevant allele before marriage and dissuading two heterozygote carriers from having children together. This is the preferred method, particularly in Roman Catholic countries, of avoiding thalassaemia, which is a huge problem round the Mediterranean. This method of preventing disease does increase the carrier population (i.e. it is dysgenic) so that it will become increasingly difficult to avoid marriage between heterozygotes. The alternative method is to allow free mate choice and to perform either ante-natal diagnosis with abortion of homozygous fetuses, or pre-implantation diagnosis with selection of unaffected embryos for implantation. These techniques have the advantage of reducing the frequency of the abnormal allele in the population (i.e. they are eugenic) but are unacceptable to some religious groups.

It has also become controversial to what extent genetic information is to be regarded as confidential and kept secret from family members, from employers and from insurance companies.

There are many genes, which are known to predispose to diseases, but with a lower penetrance, and here genetic testing is not widely done. Sometimes it is possible, knowing these genetic predispositions, to avoid environmental factors that precipitate the disease. For example those who are deficient in glucose-6-phosphate dehydrogenase should avoid eating fava beans. Furthermore, particularly in the case of the major histocompatibility complex, where alleles predispose to immunological diseases, this is almost certainly a side effect of the fact that these alleles do, or have in the past, protected against infections.

Research into genetic risk factors will provide ever more information about individual risks. Some prospects are uncontroversial, for example pharmacogenomics, where it is hoped that measuring relevant genes will predict the response to particular drugs and to their side effects, and therefore make the choice of medication more rational and safer. Some prospects are regarded as threatening. For example, if genes can be identified that predict violent, sexually deviant or addictive behaviour, the question of how this should be dealt with is highly controversial and likely to remain so. Another difficult area is the genetic prediction of serious psychological disease, particularly schizophrenia and major depression. Unless these genetic predispositions are of high penetrance, it is not clear that prevention would necessarily be wholly beneficial. One would need to be sure that one is not also selecting high ability — in the arts, or perhaps also the sciences — for which there is some evidence of an association with a tendency to depressive illness.

One important implication of the increased knowledge of disease susceptibility that genetic research will bring is the impact it will have on the provision of health services. It is fairly clear that as risk becomes better known, the use of insurance to pay for medical care will be progressively undermined. A true insurance (based on mutuality, where the premium depends on the amount insured and the assessed risk) which become unviable since both those at high risk, who will be charged high premiums, and those at low risk, who have little to fear, would do better to save their own money and pay for their own healthcare. Mutuality based insurance is essentially a pooling of unknown risk. It seems to me that the only viable and humane solutions would be a comprehensive National Health Service paid for either out of taxation or out of insurance based on solidarity (which is in fact a tax) where premiums are based not on risk but are either the same for all or based on the ability to pay.

A disappointment of great importance in the development of modern medicine is that the great successes have been – so far as chronic, non-infectious diseases are concerned – become very in the management of disease, allowing people to live lives of good quality frequently with long term medication, rather than the cure. This has led medical care to become progressively more expensive. Furthermore, while about 50 per cent of people die either suddenly or after only a short illness, the other 50 per cent require varying periods of terminal care, which in 20 per cent of

the population is prolonged. It is estimated that, on average, up to 50 per cent of lifetime medical expenditure arises in the last six months of life, independent of when this occurs. This is a forbidding statistic implying that medical advances will continue to increase the cost of healthcare. Particularly in lower income countries, it will be less and less possible to provide for most people the full extent of existing medical care. This is an intractable problem, but it is likely that society will have to come to terms with the idea that, when quality of life has become very poor, and when there are no real prospects of major improvement, terminal care should concentrate on the relief of symptoms and on allowing death with dignity rather than on prolonging life at any cost.

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Biotechnologies: Protecting the Environment, Promoting Human Wellbeing

M. S. Swaminathan

Introduction

The breathing spell provided by the green revolution for achieving a balance between population growth and food production will soon erode, unless we take steps to foster an evergreen revolution based on principles of ecology, gender and social equity, mobility and economics, employment generation, and energy conservation. In this context, a few vital national questions await answer. Will the 21st century be one of hope or despair on the food front? Will there be enough water for human, agricultural, industrial, and ecosystem needs? The present global trends in the areas of preventing adverse changes in climate and sea level and in the protection of the ecological foundations for sustainable agriculture are not encouraging. However, there is still a chance for achieving the goal of food and drinking water for all during this century, because of the uncommon opportunities opened up by science, technology and democratic systems of governance.

The term green revolution was coined in 1968 by William Gaud of the US Agency for International Development, to highlight the opportunities opened up by the semi-dwarf varieties of wheat and rice to increase production. Around the time the term first came in vogue, I had stressed

the need for concurrent attention to productivity improvement and the conservation of the ecological foundations essential for sustainable advances in agricultural productivity. I pointed out that such an integrated approach is the pathway to an evergreen revolution or sustained progress in enhancing the yield per hectare.

The forebodings that I voiced soon in 1968 are being seen today. We are witnessing an agrarian crisis due to both ecological and economic factors.

We therefore need urgent and positive steps for retrieval and progress of the green revolution of yesteryears with a view to balance population growth with food production, address the agrarian crisis and usher an era of evergreen revolution.

Food Security

The concept of food security has been undergoing refinement over many decades. After the onset of the green revolution in the late sixties, it became obvious that *economic* access to food is equally important for ensuring food security at the household level. After the World Conference on Women held at Beijing in 1995, the principle of social access, with reference to women and marginalised communities, was added to the concept of food security. Finally, after the UN Conference on Environment and Development (UNCED) held at Rio de Janerio in 1992, there has been an increasing understanding of the role of environmental factors in food security. Agenda 21 of UNCED addresses these concerns. Without safe drinking water and environmental hygiene, the biological absorption and retention of food will be poor and environmental access to food becomes important.

I define food security as a situation where every individual has the physical, economic, social and environmental access to a balanced diet that includes the necessary macro and micro-nutrients, safe drinking water, sanitation, environmental hygiene, primary healthcare and education so as to lead a healthy and productive life.

During the current century, we will have to produce more food and other agricultural commodities under conditions of diminishing per capita arable land and irrigation water resources and expanding biotic and

abiotic stresses. However, it is obvious that the pathway for productivity enhancement has to be different from that associated with the green revolution. Incidentally, it is equally important that agriculture should help developing countries not only to produce enough food for the growing population but should also lead to the generation of more income and opportunities for both skilled and unskilled employment.

I consider land, water, credit and insurance, technology-and-inputs, and market as the five pillars of the movement for agricultural renewal. An integrated farming systems approach based on concurrent attention to soil healthcare, land use planning, water use efficiency and effective post harvest infrastructure and market linkage is the need of the hour.

Integrated Farming Systems (IFS)

The eight pillars of IFS are the following:

Soil healthcare

This is fundamental to sustainable intensification. IFS fosters the inclusion of stem nodulating legumes like *Sesbania rostrata,* incorporation of *azolla*, blue green algae, and other sources of symbiotic and non-symbiotic nitrogen fixation, and promotion of cereal-legume rotation in the farming system. In addition, vermiculture composting and organic recycling constitute essential components of the system. IFS farmers are trained to maintain a soil health card to monitor the impact of farming systems on the physical, chemical, and microbiological components of soil fertility. Also, in many tropical countries, crop-livestock integrated farming systems help to conserve soil fertility.

Water harvesting and management

IFS farm families include in their agronomic practices measures to harvest and conserve rain water. Where water is the major constraint, technologies that can help to optimize income and jobs from every litre of water are chosen and adopted. Maximum emphasis is placed on on-farm

water use efficiency and on techniques such as drip irrigation, which help to optimize the benefits from available water.

Integrated crop and pest management

These are important components of IFS. These will depend on the components of the farming system as well as on the agro-ecological and soil conditions of the area. Computer-aided extension systems will provide farm families with timely and precise information on all aspects of land, water, pest, and post-harvest management.

Energy management

Energy is an important and essential input. Besides the energy-efficient systems of land, water, and pest management, every effort will have to be made to harness biogas, biomass, solar, and wind energies. Solar and wind energy can be used in hybrid combinations with biogas for farm activities like pumping water and drying grains and other agricultural produce.

Post-harvest management

IFS farmers will not only adopt the best available threshing, storage, and processing measures, but will also try to produce value-added products from every part of the plant or animal. Post-harvest technology assumes particular importance in the case of perishable commodities like fruits, vegetables, milk, meat, eggs, fish, and other animal products and processed food. A mismatch will be disastrous. Agro-processing should be promoted in villages in order to increase employment opportunities for rural youth. In addition, this can help to mitigate micro-nutrient deficiencies in diet and to promote a well-planned green belt movement around towns.

Investment in sanitary and phytosanitary measures

These are important for providing quality food both for domestic consumers and for export. To assist the spread of IFS, governments should make major investments in storage, roads, transportation as well as on sanitary and phytosanitary measures.

Choice of crops and animal components

Soil conditions, water availability, agro-climatic features, home needs, and above all transport facilities and marketing opportunities will have to determine the choice of crops, crop varieties, farm animals, and aquaculture systems. Small and large ruminants will have a particular advantage among farm animals since these can live largely on crop biomass. Backyard poultry farming can help to provide supplementary income and nutrition as also pisciculture in ponds and tanks so necessary for irrigation.

Information and empowerment

IFS is based on the principle of precision farming. Hence, for its success, it needs a meaningful and effective knowledge and skill empowerment system. Decentralised production systems will have to be supported by a few key centralised services, such as the supply of credit, seeds, biopesticides, and animal disease diagnostics. Ideally, an information shop will have to be set up by trained local youth in order to give farm families timely information on meteorological, management, and marketing factors. Field experiments organized in selected villages by our foundation has worked wonders. Organization and management are key elements, and depending on the area and farming system, steps will have to be taken to provide small producers the advantages of scale in processing and marketing.

IFS is best developed through participatory research between scientists and farm families. This will help to ensure economic viability, environmental sustainability, and social and gender equity in IFS villages. The starting point is to learn from families who have already developed successful IFS procedures. It should be emphasised that IFS will succeed only if it is a human-centric rather than a mere technology-driven programme. The essence of IFS is the symbiotic partnership between farming families and their natural resource endowments of land, water, forests, flora, fauna, and sunlight. Without appropriate public policy support in areas like land reform, security of tenure, credit supply, rural infrastructure, input and output pricing and marketing, small farm families will find it difficult to adopt IFS.

Land Use

Further developments in this regard over the last few decades include intensive research and testing. In the US, intensive research and testing of low external input sustainable agricultural practices substantially progressed. Under a project supported by the European Union, a computer model – GOAL (general optical allocation of land-use) – has been developed, which calculates optimal land-use.

The objectives incorporated in the GOAL model are :

Class of objectives	Objective
Agricultural	Maximize soil productivity
	Minimize costs of agricultural production
Socioeconomic	Maximize total employment in agriculture
	Minimize seasonal decrease in employment in agriculture environmental
	Minimize input of nutrients per unit of acreage
	Minimize input of nutrients per unit of product
	Minimize input of pesticides per unit of acreage
	Minimize input of pesticides per unit of product
Transportation	linking outbacks and countrysides with markets godowns and silos, banks, insurance agencies (for crops, cattle and farmlands) and cooperatives

Results of recent studies reveal that most land-use trends indicate that there will be a dramatic decrease in farmland. About one-third of the present area under cultivation will be sufficient once productivity in the EU reaches the optimum and, therefore, more arable land will be released for expanded cultivation. Similarly, studies at the International Water Management Institute (IWMI) have shown that nearly 50 per cent of the additional irrigation water required by 2025 can be met by improved efficiency of irrigation.

Bridging The Gaps

Our first aim should be to eliminate the widely prevalent yield-gap (i.e., gap between potential and actual yields in farmers' fields) with the best currently available technologies through appropriate packages of technology, services, and public policies. There are three major revolutions in science and technology that will influence agricultural technology in a fundamental manner. It will, therefore, be appropriate to make a brief reference to these.

- Link up villages with towns and cities.
- Speed up implementation of rural road network programmes.
- The gene revolution, which provides a molecular understanding of the genetic basis of living organisms as well as the ability to use this understanding to develop new processes and products for agriculture, the environment, and for human and animal health.
- The information and communications revolution, which allows a very rapid growth in the systematic assimilation and dissemination of relevant and timely information as well as a dramatically-improved ability to access the universe of knowledge and communicate through low cost electronic networks.
- The ecotechnology revolution, which promotes the blending of the best in traditional knowledge and technology with modern science.

In principle, these types of advances – when coupled with improvements in management science and governance–greatly increase the power of a scientific approach to genetic improvement, agronomics, integrated management of natural resources and ecosystems, and the management of local and regional development policies. However, these scientific revolutions seem to be proceeding at an ever-increasing pace, with most of the action occurring in a few places in industrialized nations. Developing countries should lose no further time in harnessing these technologies for achieving the twin goals of natural resources conservation and food security. Lately the central government in India has come round to simultaneous rural development, but the programme needs to be much more organized, pervasive and time-bound.

It may be emphasized that for launching the drive for an evergreen revolution, the arsenals of IFS will not only require enforcement but will require substantial rejuvenation.

The last 15 years have seen dramatic advances in our understanding of how biological organisms function at the molecular level as well as in our abilities to analyze, understand, and manipulate DNA molecules – the biological material from which the genes in all organisms are made. The entire process has been accelerated by the Human Genome Project, which has poured substantial resources into the development of new technologies for working with human genes. The same technologies are directly applicable to all other organisms, including plants. Thus, a new scientific discipline of genomics has arisen. This discipline has contributed to powerful new approaches that can be used in agriculture as well as in medicine and has helped to promote the biotechnology industry. Several large corporations in Europe and the US have made major investments in adapting these technologies to produce new plant varieties of agricultural importance for large-scale commercial agriculture. The same technologies have equally important potential applications for addressing food security in the developing world.

The key technological developments in this area are :

- *Genomics*: the molecular characterisation of species.
- *Bioinformatics*: data-banks and data-processing for genomic analysis.
- *Transformation*: introduction of individual genes conferring potentially useful traits into plants, trees, livestock, and fish species.
- *Molecular breeding*: identification and evaluation of useful traits by use of marker-assisted selection, which greatly speeds up traditional breeding processes.
- *Diagnostics*: identification of pathogens by molecular characterisation.
- *Vaccine technology*: use of modern immunology to develop recombinant DNA vaccines for improved disease control against lethal diseases of animal, poultry and fish.

Developing countries must exploit these techniques and develop partnerships with advanced research institutions for this purpose. There are widespread public concerns about the potential adverse impact of genetically modified organisms (GMOs) on human health and environment. Some of these concerns are genuine. In order to take advantage of recombinant DNA technologies without associated harm to human or ecological health, it is important that every country has in place suitable institutional structures and regulations for biosafety, bioethics, and biosurveillance.

Informatics revolution

New communication and computing technologies will have profound implications in everyday research activities.

- Access to the internet will soon be universal, and it can provide unrestricted low-cost access to information and techniques as well as highly interactive distance learning. The internet will not only facilitate interactions among researchers, but also greatly improve their ability to communicate effectively with the potential users of their research knowledge.
- Computing makes it possible to process large-capacity databases (libraries, remote sensing and GIS data, gene banks) and to construct simulation models with possible applications in ecosystem modelling, preparation of contingency plans to suit different weather probabilities and market variables.
- The software industry is continuously providing new tools that increase research productivity and create new opportunities for understanding complex systems of growing conditions.
- Remote sensing and other space satellite outputs are providing detailed geographic information useful for land and natural resource management.
- ICT presents a powerful tool to take the benefits of technology to the unreached. The, Every Village a Knowledge Centre, movement is making inroads and dramatically changing the lives of those it caters to, widening the threshold of opportunities.

Ecotechnology revolution

Knowledge is a continuum. There is much to learn from the past in terms of the ecological and social sustainability of agriculture. At the same time, new developments have opened up uncommon opportunities for developing technologies that can lead to high productivity without any adverse impact on the natural resource base. Blending traditional and *frontier* technologies leads to the birth of ecotechnologies with combined strength in the areas of economics, ecology, equity, employment and energy.

The decision of the World Intellectual Property Organization (WIPO) to explore the intellectual property needs, rights, and expectations of holders of traditional knowledge, innovations, and culture is hence an important step in widening the concept of intellectual property (IP). Principles of ethics and equity demand that this invaluable component of IP rights gets included when the TRIPS agreement (Trade-related Intellectual Property Rights) of the World Trade Organization (WTO) is eventually finalized. Meanwhile, the Third World including India has to take care of their interests. FAO has been a pioneer in the recognition of the contributions of farm families in genetic resource conservation and enhancement by promoting the concept of 'farmers rights'. Like WIPO, UPOV (Union for the Protection of New Varieties of Planets) should also undertake the task of preparing an integrated concept of breeders' and farmers' rights.

Precision Agriculture and Water Management

Precision agriculture involves a systems approach to experimental design and agronomic practices. It needs inter-disciplinary research, drawing on expertise in a range of subject areas such as agronomy, plant science, genetics, soil science, entomology, meteorology, weed science, plant physiology, plant pathology, ecology, and economics. Agricultural extension workers using information technology will play an increasingly important role in crop production and natural resource management. The curricula of agricultural schools, colleges and universities need to be substantially modified to make precision agriculture the road to an evergreen revolution. Precision agriculture is particularly valuable for increasing opportunities for skilled employment in the farm sector. For example, computer software

development, equipment fabrication and sales, custom hiring of software and farm equipment, local production of biofertilisers, biopesticides and drip irrigation equipment and consultancy services can all provide new opportunities for workers to become skilled.

Precision farming methods have to be based on scientific land and water use planning and need concurrent attention to natural capital stocks and nature's services. Examples of stocks include soils and soil nutrients, biodiversity, water, minerals, forests, and oceans. Examples of nature's services include water cycles, nutrient cycles, carbon sequestration, and waste recycling. Agro-forestry and other sustainable systems of land management need to be popularized in areas experiencing varying degrees of desertification. The need to conserve ecosystem services and flows under varying agro-ecological conditions through precision farming practices can hardly be over-emphasized.

In the emerging knowledge-intensive agricultural era, international cooperation is vital for taking the benefits of new technologies to those who have so far been bypassed by new knowledge and techniques. Women farmers and farm labour need particular attention in any agricultural extension and development programmes designed to reach the unreached. The gender dimension needs to be internalized in all research, educational, and development programmes intended to promote natural resource conservation based advances in agricultural productivity and production.

Sustainable agriculture in the 21st century has to be based on the appropriate use of biotechnology, information technology, and ecotechnology. Practical achievements in bringing about the desired paradigm shift will depend upon public policy support and political action. Regulation through legislation, social mobilization through local level community organizations, and education through mass media and information shops will all be needed to meet the dual demands for food and ecological security. It would be useful to consider how these concepts can be applied to water, which will be a key constraint to food and health security during the new millennium.

Conclusion

As I mentioned at the outset, food security is best defined as economic, physical and social access to a balanced diet and safe drinking water. For achieving food security at the level of each individual child, woman and man, it is essential to deal concurrently with issues relating to chronic under-nutrition caused by poverty and low-purchasing power, hidden hunger caused by the deficiency of micro nutrients in diets and transient hunger resulting from natural or human induced disasters. Hence a holistic approach to nutritional and non-nutritional factors will be necessary to achieve success in the eradication of hunger.

Science and technology can play a very important role in stimulating and sustaining an evergreen revolution leading to increases in productivity in perpetuity without associated ecological harm. Among frontier technologies, biotechnology, information and communication technology, space technology including GIS and remote sensing tools and renewable energy technology are particularly important. Nano technology is also likely to provide new opportunities. In view of the controversies relating to genetically modified foods, the following principle should be adopted to ensure consumer confidence in the products emerging from recombinant DNA technology.

The bottom line for any biotechnology regulatory policy should be the safety of the environment, the well being of farming families, the ecological and economic sustainability of farming systems, the health and nutrition security of consumers, safeguarding of home and external trade, and the biosecurity of the nation.

Transparent regulatory mechanisms should be in place if public, political, and professional confidence in GMO's is to be improved. At the same time, breeders and agronomists should work together to ensure concurrent attention to breeding and feeding crop plants for high yields. Given the right mix of professional skill, political will and people's participation, we can promote the safe and responsible use of biotechnology, nano-technology and the other emerging scientific advances. This is the pathway to an era of sustainable bio-happiness.

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The Enterprise of Science

Ismail Serageldin

How to define the domain of knowledge that we call 'science'? Along with the historian Jacob Bronowski, I define science as the enterprise by which we not only gain knowledge about nature, but also by which we organize our knowledge in such a way that it commands more of the hidden potential in nature. Science is driven by curiosity about the natural world. It is empirical and rational. It is logical.

Technology is the utilitarian application of science. It may precede science, as it did in previous times, in that people used tools and levers, because they demonstrably work, without having understood the scientific principles that underlie them. More recently, technology has been following science as new scientific insights open the door for new technologies. These in turn encourage even more research and the enterprise, which we call 'Research and Development' or R&D has been a powerful engine of progress throughout the 20th century.

For the moment however, let us focus on science as defined above. Defined thus, our discussion will remain confined to what are generally termed the natural sciences. This is not to deny the role of the social sciences or other domains of inquiry (philosophy, religion) or other domains of endeavour (music, arts). It is to delimit The magisterium of science, where a certain authority structure rules. That authority structure is the modern scientific method. Here, the authority in science is not that of an individual, it is the process of scientific inquiry, and ultimately it is empirical, measurable and falsifiable.

The classical definitions of natural sciences include: The physical sciences: (physics, chemistry); The life sciences: biology (zoology, botany); The Earth sciences (geology, astronomy, meteorology).

These classical definitions, that functioned much as separate silos for a long part of the last two centuries, have been severely challenged in the last half-century. Increasingly, discoveries have come about in the overlapping domains of science: biochemistry, paleontology, molecular genetics… to name but a few.

Furthermore, we are increasingly adopting a changed outlook, relying on process and system views, rather than isolated events or 'snapshots'. Take, for example, photosynthesis. It is now seen as drawing on different scientific disciplines in different ways. Energy, biochemical pathways, cell Biology, plant physiology, all interact to increase our knowledge of nature and nature's ways. Complexity and chaos are part of the system and can be dominant characteristics of what we confront in certain areas.

Philosophical Presuppositions

Scientists used to be called natural philosophers. As philosophers they agreed that before scientific thinking can proceed, certain philosophical presuppositions must be made about the nature of the Universe. What are these presuppositions?

- Objective reality exists – there really are things out there, everything is not simply a figment of the imagination.
- The universe is knowable – no aspects of the universe are beyond human understanding.
- The universe's operation is regular and predictable – if events occur at random, without any warning or pattern, no amount of analysis will uncover any regularity to them.

Recent advances in science are increasingly using probabilities rather than deterministic solutions. But probabilities are regular and predictable for entire groups and populations, even if the individual is subject to a level of uncertainty.

I am a believer in the theory of Non Overlapping Magisteria articulated brilliantly by the late Stephen Jay Gould. Simply stated, it is that there

are different domains of experience and thought, within each of which a certain system of authority prevails. That is called a magisterium. Human experience involves more than one such magisterium. Science is in one magisterium. Religion and philosophy are another. They are different. They do not overlap.

Science can answer questions such as: 'what is'. If you ask a question framed as what *should* I do, that is not a scientific question, and there is no scientific answer to such a question. That is the kind of question that religion and philosophy dedicate themselves to providing answers to. This is also true of questions such as the meaning of existence, or why are we alive? Or why is there a Universe? All these questions are questions to which the method of science has no answer. The magisterium of science, with its authority vested in the empirical method, does not deal with such questions.

But science and religion are not the only two magisteria. One can easily identify the magisteria of the arts. Surely how I enjoy a piece of music is neither governed by the views of science or those of religion. The quality of the music is not determined by the equations of sound or the morality of the composer or the player. True, there is now software that can recognize patterns of sound that are likely to be appealing to the public, based on other observations of music that people liked, but that is not the same as saying that people like it because of the mathematics involved. Likewise, the appreciation of the beauty of a painting is not derived from the chemical analysis of the pigments used.

Thus we must differentiate between the different magisteria when we are advancing arguments or practicing science. Indeed that is what the great scientists of the past did.

In the middle ages, it was eminent Muslim scientists who challenged the authority of the text, in that case it was mostly the authority of Aristotle that they challenged, but they specifically argued for the empirical method, and it was thanks to that approach that they advanced the sciences as profoundly as they did in the 700 years between the early 9th and 16th centuries, after which the torch of learning passed on to Europe.

Long before Francis Bacon and Galileo, Ibn Al-Haytham laid down the scientific method with rigor and clarity. Listen to his modern voice, speaking to us across a millennium of time:

> *"We start by observing reality … we try to select solid (unchanging) observations that are not affected by how we perceive (measure) them. We then proceed by increasing our research and measurement, subjecting premises to criticism, and being cautious in drawing conclusions… In all that we do, our purpose should be balanced not arbitrary, the search for truth, not support of opinions. Yet we are but human, subject to human frailties, against which we must fight with all our human might. God help us in all our endeavours".*
>
> — Ibn Al-Haytham, (965–c.1040) *Kitab Al-Manadhir.*

Centuries before Bacon and Descartes, before the emergence of modern science in the west, Ibn Al-Haytham and his colleagues issued a clarion call for the experimental method, relying on the power of observation and the application of rationality and logic. They promoted openness to the contrarian view, balanced by a healthy skepticism. They advocated prudence in running ahead of the available facts, and finally to be aware of our innate prejudices and weaknesses that may bias our work without our noticing it. This is a description of the modern scientific method, which was ahead of its time.

Ibn Al-Haytham and many others were distinguished jurists as well as scientists. Many were also theologians, but they did not confuse the two magisteria. They kept faith apart from science. This approach was also true of the great western scientists, many of whom were believers. Newton, did biblical studies, where he quoted chapter and verse. But when he did physics he abided by the authority of logic and experiment.

It is to these pioneers that we are indebted for much of the scientific advances that the world has known. They gave us the gift of the most powerful method for the accumulation and verification of knowledge yet invented by humans: The scientific method.

For many, the case of the non-overlapping magisteria is exemplified by the tragedy of the trial of Galileo. In 1633 he was forced to recant by those who insisted that science must be subjected to religion. The battles of the church and the scientific community were joined, and were to continue with science advancing and the church retreating to this very day.

The Method of Scientific Inquiry

The pursuit of science is driven by a system of thought and inquiry, and authority is vested into the system not in any individual or text. The system proceeds as follows:

- Observation of nature.
- Formulation of hypothesis to explain the observation.
- Making a prediction based on the hypothesis.
- Formulation of an experiment to test the validity of the hypothesis.
- Execution of the experiment.
- If experimental results match the expectation, then we say that the hypothesis is supported (not proven).
- If experimental results do not match the expectation, then the hypothesis is rejected and we proceed to formulate a new hypothesis.

We can thus say that the method of science proceeds in five steps: Observation, hypothesis, prediction, testing (experiment), and conclusion. *Observation* establishes some sensed specific physical realities or events. Frequently it requires measurement, and should be as objective as we can make it. *Hypothesis* formulation is making a statement that would explain the phenomenon observed. From the hypothesis there emerges a *prediction*, that under certain conditions something should happen to be consistent with the hypothesis. A prediction is to forecast a future occurrence consistent with the hypothesis. This is basic to differentiate science from speculation. It must be testable. And the test must be able to falsify the hypothesis by proving it wrong, or supporting it.

Testing, usually in a controlled experiment, which is later replicated by independent researchers, is the moment of truth: will the hypothesis be supported or will it be rejected? In some cases there is no possible laboratory experiment, but a prediction can still be tested as in Einstein's famous prediction that light from the distant stars would be bent by the sun, which was verified by measurement during the 1919 eclipse. *Conclusions* drawn from the results of an experiment or the empirical test of a prediction, is usually cautious. If the results accord with the prediction, we say that the hypothesis is supported. If the prediction is contradicted, the hypothesis is rejected and a new hypothesis must be formulated.

In addition, science seldom accepts a single result, or the unsupported claim of a single researcher. It requires verification through replication of the experiment and its results by other researchers.

Thus a 'scientific fact' is merely an observation that has been sufficiently and repeatedly confirmed to be considered for all practical purposes to be 'true' even though the possibility of some new experiment falsifying it remains open.

That is what Albert Einstein meant when he said:

> *"No amount of experimentation can ever prove me right. A single experiment can prove me wrong."*

Now the contours of the magisterium of science, where authority rests with a method rather than an individual or a text, can be better ascertained. Scientific knowledge is, for all intents and purposes, approximate, in so far as it is not a definitive description of nature or nature's ways. Indeed, science in the last century has taken us into realms of the very vast and the very small where empirical and replicable evidence supports phenomena and interpretations that we consider unusual when judged by 'common sense' derived from our experience of nature at our scale and with our five senses. Every new discovery added something to the previous efforts, or falsified one of the assumptions under which scientists had been labouring (a static Universe, an atom that is the smallest unit of matter, etc.). Gradually a more convincing and more complete image of reality was being formed and still is in the process of being formed. That is why scientific knowledge is approximate and it remains potentially falsifiable by a new idea and experiment.

Terminology in Scientific and Social Discourse

Terminology in science can be somewhat different from the conventional everyday use of the same words. This can be seen when we review the scientific meaning of the following words: fact, truth, hypothesis, model, theory, and law. Each of these words is assumed to have the same meaning in scientific discourse as they would have in social discourse. Actually, this is not correct. Thus, for scientists, we can define these words as follows:

Fact: An observation that has been repeatedly confirmed, and is accepted for all practical purposes to be 'true'.

Truth in science is never final, and what is accepted as fact today may be modified or even discarded tomorrow.

Hypotheses: A hypothesis is a tentative statement about the natural world leading to deductions that can be tested. Hypotheses can be verified or rejected by tests or experiments. Hypotheses can be used to build more complex inferences and explanations

Models, usually in today's world, models tend to be mathematical representations of reality. Thus a model is another form of hypothesis, as it is also a tentative statement about the natural world leading to deductions that can be tested.

Law: A descriptive generalization about how some aspect of the natural world behaves under stated circumstances.

Theory: A well-substantiated explanation of some aspect of the natural world that can incorporate a large body of scientific facts, laws, logical inferences and tested hypotheses.

Contrary to common parlance, where the adjective 'theoretical' or the noun 'theory' is used to mean something that is unproven and speculative, the word theory is used in science to mean a very powerful and well-substantiated proposition (or set of propositions) that has been tested empirically, and found to be robust and to have strong explanatory power.

Thus we talk of the Theory of Relativity, or Quantum Theory. These are the most rigorously tested and most powerful theories in science today. Likewise, evolution is one of the strongest and most useful scientific theories today.

Scientists are creating the magisterium of science by their work and the adoption of a set of values that allows the scientific method, not a person or a text, to be the final arbiter of their contributions.

The Values of Science

The values of science are those values without which no real scientific research can be practised. These are the same that were so eloquently described by Jacob Bronowski in his classic work: *Science And Human Values* published more than a generation ago.

Truth: No scientist would ever be forgiven the reporting of false data. Mistakes in interpretation are one thing, but falsifying data is unforgiven in the community of scientists. Sir Cyril Burt was struck down from the annals of cognitive psychology posthumously when this was discovered about his work.

Honour: The second most heinous crime is plagiarism. An elaborate system of footnotes and reference citation is maintained in the arsenal of scholarship. Giving due honour where honour is due is fundamental.

Constructive Subversiveness: Science advances by having a new paradigm overthrow the old, or at least expand its applicability in new ways. Thus inherent in the scientific outlook is a willingness to overthrow the established order of thinking, or else there will be no progress. Frequently, those who come up with new insights are remarkably young. Einstein was 26 when he wrote his five papers in 1905, and Dirac was in is twenties when he hypothesized anti-matter, and so on. This means that seniority cannot rule unchallenged.

Tolerance and Engagement: The very openness of science to the new, means that there has to be tolerance for the contrarian view — provided that it can be backed up by evidence or subjected to rigorous tests of replication and meet the falsifiability criterion. This principle, formulated by the philosopher Karl Popper states that the scientific method requires that a hypothesis be stated in such a form as to allow its testing by an experiment that could falsify it, or prove it wrong. If it cannot be so formulated, then it is speculation and not science.

Note for example, that Einstein's theory of relativity postulated a constant speed for light in a vacuum, explained the perihelion of Mercury and predicted the bending of light passing near the Sun. These revolutionary ideas from a young unknown scientist explained a lot of observed phenomena, but could they be wrong? It was the verification of the predicted bending of light passing near the Sun by expeditions studying the total eclipse of 1919 that gave the theory enormous support.

Likewise, the elegant mathematics of the young Paul Dirac predicted anti-matter. Dirac later won the Nobel prize when still in his 30s.

Unusual ideas coming from young-unknowns can turn out to be the new breakthroughs that the scientific community has been searching for. This means that scientists must remain tolerant and engaged. In that sense the tolerance based on the adoption of the values of science is different from the tolerance of political liberalism, which may mask indifference to the behaviour of others, dismissing them without engaging them. Tolerance among scientists requires respect for the contrarian view and a willingness to test unusual ideas against the rigour of proof.

An Established Method to Settle Disputes: Scientists everywhere are willing to accept the arbitration of disputes by the testing of hypothesis and accumulation of evidence. The larger the claim, the more compelling the evidence must be. But the appeal to reason, to debate and to the rational interpretation of evidence is overwhelming in the scientific community.

Imagination: We value the imagination of those who break the mould, and open new vistas, not just those who add at the margin. Thus the ability to pursue the new, to respect the contrarian view, are important parts of the scientific enterprise. Science values originality as a mark of great achievement. But originality is a corollary of independence, of dissent against the received wisdom. It requires the challenge of the established order, the right to be heard however outlandish the assertion, subject only to the test of rigorous method.

Thus as Bronowski said: Independence, originality and therefore dissent — these are the hallmarks of the progress of contemporary science and contemporary civilization.

In parallel, the scientific community has learned to be wary of bias for its corrosive effects on the practice of science. Scientists now rightly decry the racial biases of even eminent scientists such as were manifested by Paul Broca in his brain studies, or of anti-Semitism in all its guises. Yet, we still have to recognize the inadequacy of the scientific community's response to gender bias.

Institutional Arrangements in the Conduct of Science

The enterprise of science requires the interaction of a complex set of institutions, with each performing a particular function. If the enterprise of science in developing countries is to flourish in this new century certain institutional arrangements will have to be implemented. In general these not only include the close ties between S&T and R&D, but also the active presence of a number of these institutions that must interact to create the climate of scientific research and link it with technology through R&D. These institutions are:

The Academies of Science: these are independent member-driven organizations whose function is the promotion of science, the scientific outlook and excellence in science, all for the benefit of humanity. In some developing countries these institutions exist but have been totally taken over by the state or by small elderly elites that will not allow younger members to join. In others they do not exist at all. Yet their existence and their vibrancy are essential to ensure that the values of science thrive and that S&T can have a place in the development of a country. Academies of science should also have strong ties to academies of engineering, agriculture and medicine, three fields where the scientific enterprise interacts most directly with the public at large.

Autonomous Centres of Excellence. these address local challenges. Science and engineering advance largely at 'centres of excellence' — physical locations where research and advanced training are carried out, often in collaboration with other centres, institutions, and individuals. Centres of excellence are the key to innovation, and their importance cannot be overestimated. For the S&T capacities of developing countries to grow, therefore, they too should have centres of excellence — whether of local, national, regional, or international status. These do not necessarily have to be created *de novo*. The bolstering or reform of a country's most promising existing R&D programmes can achieve the desired outcome. A key to promoting excellence is merit-based allocation of resources based on rigorous review, both in deciding on new research projects and evaluating current programs. Given the relatively modest scientific capacity of most developing nations, such reviews should ideally include appropriate experts from other nations.

Centres of excellence — whether of local, national, regional, or international status — should be created, or seriously planned for the near future, in practically every developing country in order for its S&T capacity to grow. They can serve as the main nodes for individuals or groups charged with enhancing S&T knowledge of national and even regional importance. The centres should have institutional autonomy, sustainable financial support, knowledgeable and capable leadership, international input, focused research agendas that include interdisciplinary themes, applied research as well as basic research, technology transfer, peer review as a systemic element, merit-based hiring and promotion policies, and mechanisms for nurturing new generations of S&T talent.

- Where such institutions already exist, they should be reinforced or, if necessary, reformed. When reform is indicated, changes should be system-wide and carried out in ways that make best use of scarce resources (including the local talent).
- New scientific and technological research projects should be decided on the basis of input from expert review, with each project and program evaluated both for technical merit and its potential benefits to society. All existing research programs and centers of excellence can similarly benefit from periodic expert review and evaluation. Techniques for such procedures should include, as appropriate, peer-review teams, relevance-review panels, or benchmarking studies.
- Given the relatively modest scientific capacity of most developing nations, their merit reviews should ideally include appropriate experts from other nations. Such involvement of the global research community, possibly through a program of international cooperation among academies of science, engineering, and medicine, can make the merit-review processes in developing nations more effective—and not just for particular programs but in general.

Strong Universities. These are critical for expanding national S&T capacities. The role of universities in the development of S&T capacities cannot be overstated. Universities educate and train new generations of S&T talent, perform research and development on issues of importance to the nation, and provide an independent source of information on such topics as economic development, agriculture, health, and the environment.

National governments in developing countries should make a clear, continued commitment to support and encourage advanced education and research activities within universities, in partnership with independent research institutes and industry. Without an explicit national commitment to strengthening universities, the goals of attaining a critical national capacity in S&T cannot be achieved.

- National and local governments in developing countries should strengthen higher education with public funds (supplemented with private funds if available) to offer greater opportunities for tertiary education and S&T-training to young people in modalities ranging from community colleges (as they are called in the US) to top-class research-based universities.
- National and local governments in developing countries should develop strong partnerships with universities and industry to plan the development of capabilities in science and technology.
- Universities should have increased autonomy while seeking to systematically strengthen their ties with regional and international institutions and networks; such links can significantly increase the effectiveness of the universities' science and technology efforts.
- Research universities should make strong commitments to excellence and the promotion of the values of science in their activities, incorporating unbiased merit reviews into all of their decisions on people, programs, and resources; they should also have greater interaction with society at large.

Virtual Networks of Excellence. These link the scientific talents of entire regions and the globe. An important step toward building centers of excellence will be the creation of Virtual Networks of Excellence (VNEs), extending throughout the developing world, with the primary objective of nurturing scientific and engineering talent in mostly 'virtual' science and technology institutes. These entities should be relatively small, efficient, and embrace innovative research groups that may be far apart geographically but closely linked via the Internet and anchored in recognized research centers. The VNEs' institutes will work to blend their activities into coherent programs, yet the individual research groups will work in areas of prime interest to their own countries. Successful examples of VNEs are the Millennium Science Institutes created in several countries by the Millennium Science Initiative with the support of the World Bank.

International institutions such as TWAS, IAP, and ICSU. These should help in the formation and strengthening of nascent national and regional institutions. The participation of these international bodies will help new organizations establish the requisite high standards and effective mechanisms of operation.

Without a critical mass of active scientists or engineers in a country, the creation of such academies is not possible. In such cases, these institutions should be built on a regional rather than national basis.

It is essential that the academies actively participate in national and international debates in order to make the voices of science and technology heard on a broad range of issues.

Digital libraries of S&T. These can bring knowledge to virtually everyone, everywhere. Scientists and technologists in developing countries have limited access to recent research findings (mostly in journals), to reference materials (mostly in libraries elsewhere), and to databases (some of which are proprietary); and these problems have been exacerbated in the last decade as information streams turned into torrents. The enormous advances in information and communications technology (ICT) have opened up opportunities for remedying the situation as never before, though these same advances have also raised issues of intellectual-property rights. The proper harnessing of digital technologies is essential to S&T capacity-building in the developing countries, which should make major efforts to provide adequate ICT infrastructure and trained technical personnel for their learning and research institutions.

- Efforts to provide digital copies of back issues of scientific and engineering journals should be intensified, and the full range of these materials gradually posted for free and universal access, starting with S&T professionals in developing countries.
- The print journals presently publishing should be encouraged to post selected articles in electronic form concurrently with their paper publication; and to reduce the time between the appearance of the latest issue of the journal and its posting.
- A major international effort should be launched to ensure that a digital-format basic-science library is made available to libraries in developing countries.

- As much as possible of the scientific, engineering, and medical literature should be put in digital form on the World Wide Web for access from remote areas. In that spirit, new approaches should be explored for replacing copyrights with more suitable ways of protecting IPR and rewarding innovators, while supporting the public interest in having broad and rapid access to knowledge.
- Major hubs in the developing world should be organized for sharing digital information with research institutions in the industrialized world. This will facilitate access to some materials (in video format, for example) that require large bandwidth not necessarily available everywhere. It will also serve the eminently sensible goal of backing up original material.
- Libraries should maintain electronic gateways for the sharing of digital information among researchers, teachers, and learners.

Conclusion

The scientific method is central to the enterprise of science. Without it there can be no real R&D, no technologies. Those who would compete in the 21st century must develop their capacities in S&T. It is a necessity, not a luxury. They must become producers of knowledge, not just consumers of technology. The world will pass them by if they do not master the new knowledge of the new science in order to harness the new technologies of the new century. That will require an interacting set of institutions that can nurture a people's talents and allow the space of freedom necessary for creative individuals and dedicated scientists to make their contribution. All of that, however, requires that people understand that there is a magisterium for science, where authority rests with the scientific method, not with a person or a text. That this magisterium of science is separate from those of religions and philosophy and of art and music. That the enormous benefits of science and technology will not accrue to those who will not allow tolerance of the contrarian view to flourish, and allow the scientists of tomorrow to make their contribution to creating a better future for all.

16

Prometheus and the Internet: A Science Supercourse for the 21st Century

Ronald LaPorte and Ismail Serageldin

"Education is the most powerful weapon which you can use to change the world".

— Nelson Mandela

Background

Today, 80% of the World's populations are still living deprived of quality on line or on time access to the most relevant scientific information that could help change their lives.

Today, teachers of science in many of the developing counties do not have the tools or the means to present to their students science in an effective fashion, thus keeping them and their students distant from the science of today.

Promoting the values of science, with all they mean for the promotion of tolerance, rationality, creativity, the search for truth, adherence to codes of behavior and a certain constructive subversiveness. This last, is because it is essential in science to be able to listen to the contrarian view, and accept or reject it on the basis of empirical evidence. Science and the

scientific enterprise also create a forum for the exchange of ideas and the arbitration of disputes that has served humanity extremely well in the last few centuries. Promoting the values of science are the best investment in fighting obscurantism, fanaticism and xenophobia and they help promote the capacity to embrace diversity and to cooperate across different cultures, races and religions.

Beyond the ideas of teaching science and mathematics, there are at least three fields of obvious interaction between people and science, which go beyond research into application, beyond the theory to the applied, and these are: Medicine (and Public Health); Agriculture; and Engineering. In these three fields, the practitioners apply science, and frequently deal with clinically observed approaches, even if they are not yet sufficiently understood scientifically. Furthermore, the environment, is a domain where do-gooders with limited understanding, are now giving way to an impressive body of scientific knowledge that should help inform the actions of governments, institutions and individuals.

In these four domains of Medicine and public health; agriculture; engineering; and environment, there is enormous benefit in being able to provide a lot of up to date information to the rest of the world in real-time. Here is where the proposed Supercourse approach, with Just-In-Time (JIT) lectures and knowledge delivery systems can be of enormous help to:

- help build ties across nations and expand the community of science across "silos" of specific disciplines and sub-disciplines;
- help provide badly needed information to people who can use it to combat poverty, disease, hunger and malnutrition; and
- provide quality, Just-in-time (JIT) materials to assist those who are dealing with crisis situations.

The Means are at Hand

Using internet based approaches, and relying on the ubiquity of PowerPoint presentations all over the world, we propose to establish communities of practice in the various areas of science, starting with the four domains mentioned above.

The concept we are discussing has been tested successfully in at least one domain: Epidemiology, Prevention and public health. Recent efforts showed also that the concept of JIT lectures materials were enormously helpful in crisis situations.

This experience is more than a "proof of concept" it is a case study of a major return on very limited investments of public funds largely through the commitment of a few learned individuals and the positive reaction and participation of thousands of individuals all over the world who were moved by the vision and enthralled by the content of the material. Ultimately hundreds of thousands participated and millions benefited. This case study, which started in epidemiology, deserves to be presented in more detail, as it shows what can be done, and establishes the credibility of the present proposal, and of the individuals advancing the proposal.

The Experience So Far: Supercourse, Global Health, and Information Sharing

A new system for our times

Prevention education is the most powerful weapon which can improve the health of the world. However, in the world of health there are health knowledge "haves" and "have nots". During the past few years we have been developing a new system for global training in prevention, making shared networks and knowledge available to all, especially to reach the unreached with state of the art scholarly global prevention knowledge. It has been our mission to build and distribute high quality prevention knowledge to the teachers of the world, and we are succeeding. It also our goal to establish new boundaries for global education.

Global health network and the Supercourse

We have used the Internet to network together 30,000 faculty from 151 countries. The network is used to collect the best possible PowerPoint lectures on prevention, and to share these lectures among this group and the world (www.pitt.edu/~super1). We have been very successful in obtaining 2358 lectures. These have come from 6 Nobel Prize winners, and 60 members of the Institute of Medicine. This is a powerful tool

of global diplomacy as we have 1800 members from Muslim countries, 500 from the Former Soviet Union (FSU), and 5000 from the USA all working as scientists and scholars. It has been stated that the project is a "noble cause", with equality, and sharing on the most precious resource of scientists, our knowledge. Our plan is to empower the teachers of the world, by offering them this material and the support of this community of practice.

The program is not driven by developed countries. We have outstanding lectures from developing countries such as Avian Flu from Pakistan and the Philippines, West Nile fever from Egypt, and Iodine supplementation from India. We share the knowledge among ourselves and with others. It is "open source" in that copy right is held by the authors. The authors agree to make their lectures available for free. The lectures have been distributed with 42 mirrored servers (copies of the lectures) in the Sudan, Mongolia, Russia, Egypt, and elsewhere. The lectures are distributed on CDs. We provide these to people with the understanding that this is a gift meant to be given. We ask them to copy the CDs for at least 5 people, preferably students. Over 50,000 centers world wide have a CD of the Supercourse. The Supercourse now is one of biggest and best known global health projects. The network of collaborators includes the Library of Alexandria, as well as over 5000 universities world wide.

Best scientists, best lectures reaching the most people

We are in an age where we can start to bring the best possible materials to the teachers and students of the world. We are demonstrating this with the "Cutler Lecture" which is the most important international health lecture at the Graduate School of Public Health in Pittsburgh. Eric Noji, M.D., a leading expert on disasters, gave the lecture. We decided to reach a million people with the lecture world wide. To do this we had Eric present his lecture at the University. We used a multi-channel approach with his lecture being broadcast using web casting, and web archiving. His lecture is also available using I-pod technologies. With these methods Eric himself teaches world wide. In addition, his lecture is available using .ppt , .pdf technology and Supercourse technology for teachers to down load. In addition, we used a viral marketing strategy by sending out the lecture to 30,000 people and asking them to forward it to others. Our goal

is to make the lecture available to high bandwidth Silicon Valley, as well as low bandwidth Sudan. It proved to be successful, in fact too successful. For his presentation we set the limit for the hour of 500 links coming in as we figured that most of the links would be from classes of 50 faculty and students. We were enormously surprised that for that hour 2500 links visited, representing perhaps 100,000 people. There were people in Tehran at 2 in the morning, some in Beijing and people elsewhere in China as well.

This was a very important exercise as we found that there is a huge demand for good prevention information, and that we could deliver this in almost ever country using web casting. Many teachers could not be reached immediately, but they could through CDs, and putting the lectures into slides, overheads or paper. There is no question in our minds that we can reach a large percentage of teachers in the world using multiple channels. The teacher is critical to help his/her students assimilate the provided material that may come from a scientist with a different culture or frame of reference.

The work originated in Pittsburgh, but the Supercourse and the Library of Alexandria work closely together. The Library has distributed thousands of CDs containing the Supercourse. The Supercourse also has a lecture on the Library of Alexandria. We want to build a bridge between East and West and have worked closely to build a Muslim Scientific Supercourse of 1800 individuals closely interacting with the US and the West. A copy of the Supercourse is on the Library of Alexandria server and the Pittsburgh and Alexandria teams work closely together. We have build a unique public health diplomacy going from east to west and from west to east.

Some facts and figures

The Supercourse consists of:

1. **Open Source:** Global faculty share their best PowerPoint lectures on prevention. Experienced faculty member beef up their lectures with little struggle. New instructors reduce preparation time with better lectures. Faculty in developing countries use current scientific template lectures to build their own.
2. **"Coach" Educators:** The Library of Lectures consists of exciting lectures by scholars in prevention. The classroom teacher "takes"

them out for free. Faculty who contribute lectures will shortly answer questions through a global help desk.

3. **Teaching Faculty:** Six Nobel Prize winners, 60 IOM members and other top people contributed lectures. Almost half are from outside the US.
4. **Mirrored Servers:** We have 45 mirrored servers in Egypt, Sudan, China, Mongolia and other places.
5. **Free CDs:** We have distributed 20,000 Supercourse CDs.
6. **Multiple Channels:** In addition to PowerPoint we are using multiple knowledge channels to share information including web and pod casting.
7. **Teaching a Million:** The best teachers should produce the best lectures to teach thousands if not millions. We tested this with our disaster lectures and likely will reach a million students with a single lecture.
8. **Just-in-Time Lectures:** We created scholarly lectures within days after the Bam Earthquake, Kristina and Rita, and Avian Flu. We "drilled" these into the classrooms of the world, reaching 120 countries.
9. **Quality Control:** There is very little scientifically based and effectively administered quality control in education. We have been exploring scientifically based quality control from other disciplines.
10. **Global Health Society:** We are building a global health society which will include a journal and meeting.
11. **Global Health School:** We are creating some new models for Global Health Schools. These are – like the "Honda CRX" — inexpensive, small, but of high quality, nimble and sustainable.
12. **Progress:** We published over 170 papers in journals including Nature, Lancet, BMJ, Nature Medicine, PNAS among others. Our web pages have been identified as in the top 100 by PC Magazine. We receive 75 million hits a year and likely will help teach over a million students. We are the largest suppliers of lectures of Global Health in the world.

The future

The Supercourse uses the power of the local classroom teachers and enhances their ability to teach. The goal is to provide the best possible template lectures over the Internet using Open Source system to "beef

up" the lectures world wide. This improves teaching with less struggle. We scientists help scientists with out expensive middlemen publishers. We already see enormous success with thousands of instructors, the teaching of up to a million students with a single lecture, and the collection of the best scientific teaching materials on prevention.

We see this as an important means to bring the top experts of the world to the table, and have them work together. Scientists want to collaborate across their boundaries and we have establish a means by which this can occur. The future of all of our countries is our health and our children. We can train students now so that we all will live longer and more productive lives, by making accessible and sharing the prevention knowledge of the world.

Helping in Crisis Situations: Just-in-Time (JIT) lectures

We discovered the power of JIT lectures during the Bam Earthquake in Iran. This also brought Ali Aralan into the Supercourse. Days after the Bam Earthquake we created a lecture by one of the most important persons in global disasters, Eric Noji, M.D. Within days after this, Ardalan from Tehran created a wonderful lecture on the Bam Earthquake which was used world wide.

We discovered that most disasters had a "prodrome". This is a period of time before which the major effects of a disaster are felt. For example, the twin hurricanes in the US had a 4-5 day period before they struck land. During this period we reasoned that we could rapidly establish a lecture, and make it available. As soon as the Katrina was on the radar, Ali Ardalan from Iran, and Ronald LaPorte contacted 30 meteorologists world wide. Within two days, with their help, a scholarly lecture on "What is a hurricane" was created. We did this as people of the world were obtaining their public health and meteorological information from CNN and seeing dead bodies floating, and crushed houses. Our concern especially was what we call the "epidemiology of fear" whereby much of the damage to a country from a disaster likely comes from fear to those who were not directly affected. We were able to find people who could send the lectures to all the schools in Texas and Pennsylvania, and to all the epidemiologists in Texas, as well as 42 of the 50 states. Just-in-Time lectures are very powerful method to educate students about earthquakes.

We did exactly the same thing with the earthquake in Pakistan. Ali Ardalan from Iran prepared a beautiful scholarly lecture on "what is an earthquake" (see www.pitt.edu/~super1/). Khawar Kazmi, M.D. undertook to distribute this to the schools of Pakistan. There are 54 million students. We think we can reach several million of them. This is more of concern as Pakistani television continually showed crushed schools, and kids being pulled from the rubble. Kids are scared of school, and they need not be. Our lecture presents the science, showing how earthquakes develop, and also showing that although deadly, one is 40 times more likely to die of a heart attack and that any one year a child has one chance in 300,000 in dying in an earthquake. This is not to downplay the importance of earthquakes, but is important for students to know their actual risk, to counter the fear driven by the images in the media with a more rational assessment of the real level of risk.

Towards A Global Science Supercourse

The scope of the proposed effort

We have been highly successful in improving training, research and collaboration in our chosen Public Health discipline, with tens of thousands of academic faculty and the largest collection of scholarly scientific presentations on disease prevention in existence. Why cannot we expand this to all of science and have a million faculty and 300,000 lectures helping each other? Why not put into the Supercourse PowerPoint lectures of our recent publications? If this were possible then we could start to melt our scientific silos, thus epidemiologists could teach students about the chemistry of water pollution, chemists could teach about the marketing of products, and researchers in the Gobi desert could teach their students about the formation of snowflakes. In addition we can reduce the scientific divide between the haves and have nots. We can also reduce the speed by which scientific information comes into the classroom from 7 years to 7 hours, or even 7 minutes.

We would use exactly the same approach as with our Public Health (epidemiology) Supercourse. The first step would be to network scientists in different communities of practice, as far as we can world wide. The

second step would be to extract and share their best PowerPoint lectures. The third step would be to present them in a coherent framework.

We recognize that there are those who would have substantial fears that astrology would find its way into astronomy lectures, or that creationism would slip into evolution or biology lectures. However, two very real examples should assuage these fears. First, the experience of the epidemiology public health Supercourse is there for us to evaluate. It has been quite successful in maintaining very high standards. The second example is even more dramatic: Wikipedia, has hundreds of thousands of articles and has succeeded in maintaining quality by mobilizing the communities of practice to review articles and maintain quality.

Socrates was right, "there is only one good, knowledge, and one evil ignorance". With a Scientific Supercourse we can revitalize the teaching of science in the world and empower future generations of young Scientists.

Replicating the successful experience of the Health prevention Supercourse and extending it to other domains, will require slight changes in the way we can move from a single field where the initiators were international experts of the highest caliber, self-selected into creating the teams that pushed this forward. They combined scientific expertise, internet savvy, and a remarkable ability to network. These key individuals were critical to the success of this enterprise. Other individuals with similar attributes will have to be identified and mobilized in other domains. It is not immediately obvious that those who volunteer their services will necessarily be the best suited to the tasks. We must also be able to screen and weed out astrology from astronomy, numerology from math, creationism from evolution. Yet we do not want to lose out on the enthusiasm of young researchers around the world who may have both the time and willingness to participate in such a venture.

Organizing for implementation

It is thus proposed that we have a general committee of experts to guide the overall growth of the enterprise, anchored in several institutions around the world. The operative word is "guide", not "administer". The activities themselves would be based on three concentric circles, starting from the broadest to the central:

The general participants contributions: This is like the Blogosphere. It is volunteered material from many which may not be vetted and where

some discernible future patterns may later emerge. It encourages activism and participation from all over the world, but may contain errors and downright lies (intentional or unintentional). Remember that a head of state was once pushing a view that HIV is not the cause of AIDS.

The Knowledge Sphere: This is information divided into "domains of knowledge", each governed by an identified "community of practice", as happened in the case of the health prevention. The material in the knowledge sphere is either produced by them or approved by them. They will also organize the overall structure so that people can find material more easily and navigate this particular "domain of knowledge". Each community of practice will have one or more individuals acting as anchor(s). These anchors must be eminently recognized individuals in their fields with known institutional affiliations. They may be members of the committee of experts or at least will be in touch with them. For purposes of our vision, these have to be the best possible people willing to give the best possible lectures.

The Select (Golden) Lectures: These are the best of the best, in each domain, from introduction to science to highly specialized lectures. To these we can hope to give the same treatment given to the Eric Noji lecture in the case of health. These will be selected by the communities of practice and the anchors.

Outputs

Based on our previous experience, the outputs of this proposal are:

An International Portal for Activist Science: From science education to crisis management, an enormous amount of posted information, organized into coherent domains of knowledge, will be available and searchable and downloadable for free. The Library of Alexandria, known as the Bibliotheca Alexandrina (BA) is ready to host this portal and maintain it. The BA had just formally joined the Digital Library Federation, a group of some thirty institutions that include the Library of Congress, MIT, Caltech, Stanford, Harvard, Yale, and thus has the wherewithal to undertake this task. The BA is also collaborating with the French Academy of Sciences to Arabize the portal "Main a la pate" (Hands on Science for young people) and will host that portal as well.

Communities of Practice: in every domain, in every country in the world. Networked communities of practice will be engaged in the promotion of science and education, using the tools of the 21st century to address the global problems of ignorance, poverty, disease and malnutrition. These linked thematic communities of practice will become a a network of networks, a very powerful tool for the promotion of international collaboration in many fields.

Crisis teams: drawing from different communities of practice and building on experience it will be possible to create crisis teams to address the needs of different crisis situation from around the word. These will include combinations of scientific/technical expertise and ICT expertise. The presence of such teams means that we will also build on shared experience from different crisis situations to become ever more effective.

Golden Lectures: A selection of the best of the best lectures that result in millions of people being able to have the experience of attending such an event, and the storage of such videoed lectures for others, will over time create a great educational legacy. Here the goal is to create multiple channels of lectures which include web casting, video, web archiving, PowerPoint, pod casting. The more channels we have, the easier it is to cross the digital divide

Derivative materials: From the crisis situations and the communities of practice as well as the golden lectures, we will have important inputs for people who may want to make movies and documentaries for broadcast through television.

Distribution systems to schools: Our mission is to reach the teachers of the world with very high quality lectures to be used in their classrooms. We will establish an internet based supply chain which will be a end-to-end solution to bring the best possible global scientific materials into the classrooms of the world

Sustainability

The international communities of practice will be the guarantors of continuity and sustainability as they evolve and grow, and new members join their ranks. The cost of collection and delivery of materials will be very small in relationship to the numbers of teachers who will use these materials. Delivery of materials to any school will probably be less than

the cost of a single text book. We envision that this system could tap into the global library systems of the world with the Library of Alexandria taking the lead. They will be renewed by new generations of members. Sponsoring institutions will help (see below).

Getting started and sustainability

A the epidemiology experience showed, it is better to start with domains where there is existing and willing expertise, and where at least an embryonic international network exists. This will ensure that the minimum conditions for growth are there for when the initial impetus is given. Whether we start with two, three or seven or ten communities of practice would depend on these initial conditions.

These should be announced with a proper launch event, highly publicized and inviting the participation in this open collaborative effort, with minimal screening. The community of practice would gradually and gently handle the quality control issues.

Build a consortium of sponsoring institutions: Here we could follow a DLF or JSTOR type business model: one time fee to become a sponsor plus a smaller annual fee to support the program.

Envoi

If these be dreams, let us salute the dreamers. Were it not for dreamers, men would be still living in caves. In the exciting world of the new century, of the Internet and of instant communications, or plentiful knowledge and willing minds and hands across the planet, is it conceivable that basic knowledge of science should remain hostage to those who control books and textbooks and those who have the means to buy them? Surely, we can do better for the 80% of humanity that is presently inadequately equipped to participate in the exciting scientific and technical revolutions of our time. As they are empowered to provide such material into every classroom, the younger generation of students will be better able to take charge of its own destiny, to harness technology to its needs and to become real producers of knowledge, not just consumers of technology. This is a future that is within our grasp. We intend to do our part to make it happen.

4

BETTER HEALTHCARE FOR ALL

17

Infectious Diseases and the Disease Control Priorities Project (DCPP)

Joel Breman, Dean Jamison, George Alleyne, Adel Mahmoud

Introduction

The Disease Control Priorities Project (DCPP) is an alliance between the Fogarty International Center, US National Institutes of Health; World Bank; World Health Organization; Population Reference Bureau and the Bill & Melinda Gates Foundation. Its aim is to derive, create and disseminate information for rational health decision-making in low-and middle-income countries (LMIC). The DCPP has developed an evidence base by:

1. Defining disease burdens.
2. Using cost-effectiveness analysis for single interventions and packages.
3. Summarizing control and eradication programme implementation experiences.
4. Identifying areas for further research in support of disease control.

The overall objectives of DCPP are to decrease illness, disability, death, and economic burden by stimulating national priority setting

and the development and implementation of programs based on local information and resources. In 2006, DCPP published two landmark books, *Disease Control Priorities in Developing Countries, 2nd edition* and *Global Burden of Disease and Risk Factors*, and a companion tome, *Priorities in Health,* which summarized the results of four years of research, consultations, working papers, and contributions of over 350 authors (Jamison et al., 2006; Lopez et al., 2006).

The first edition of the World Bank's *Disease Control Priorities in Developing Countries*, published in 1993, and the *World Development Report 1993: Investing in Health* became standard references for health policy makers. The *Global Burden of Disease*, published by WHO in 1996 summarized, for the first time, the toll of all major diseases, by geographic region, using a new metric, the Disability Adjusted Life Year (DALY), which defined burden in terms of healthy life lost to disease (Murray et al., 1996). These earlier documents had a more limited scope than the current volumes and research issues were not examined. Most importantly, epidemiological and economic profiles of the topics considered in the early nineties had changed considerably, as had disease trends and interventions, meriting this new comprehensive analysis.

Background

There have been great strides in improving health over the latter half of the last century (Deppen, 1999). Gains in life expectancy in developing countries are most striking, especially in China. Demographic and epidemiologic transitions show that populations are aging in both low and high-income countries. Non-communicable diseases are rapidly gaining importance requiring immediate definition, and planning for control and research. The exceptions are countries in sub-saharan African and, to a lesser extent, South Asia where communicable diseases still reign and which have the lowest gross national income (GNI). Life expectancy in ub-aharan Africa has decreased recently due in great part to the HIV/ AIDS epidemic.

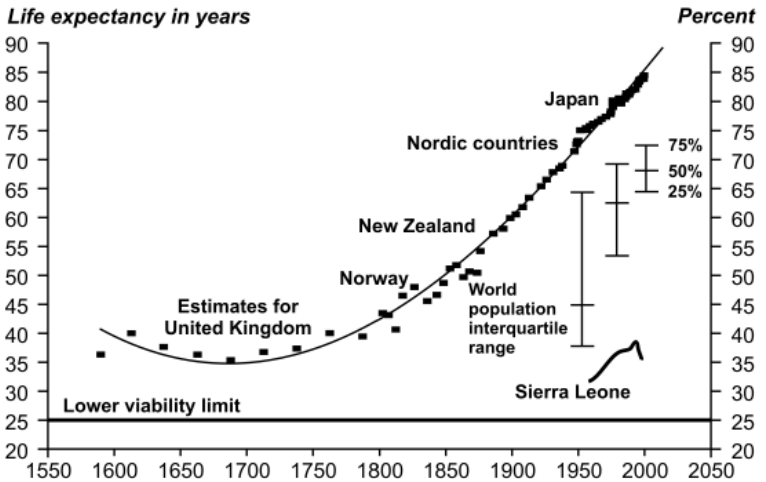

Figure 1. Life Expectancy Since 1550 in Selected Populations and in the World and Sierra Leone Since 1950
Source: Deppen 1999

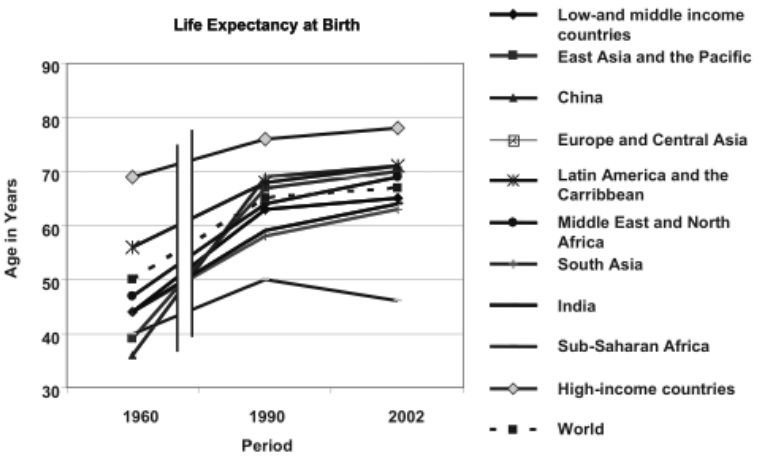

Figure 2. Disease Control Priorities Project (DCPP) Levels and Changes in Life Expectancy, 1960-2002, by World Bank Region
Source: Disease Control Priorities Project. Burden of Disease in China in 2001 (http://www.dcp2.org/pubs/DCP/1/Table/1.1)

Major Findings

Burden of Disease

LMICs comprise 85 per cent of the world's population and 90 percent of the burden of disease (Table 1). The five major burdens of disease in LMIC and high-income countries are shown in Table 1 by World Bank region (Mathers et al., 2006 and Lopez et al., 2006).

Table 1. Disease Burden by Income, 2001

Countries	Population in millions (%)		Disability-Adjusted Life Years (DALYs)				
			For all diseases, no. in millions (%)		For infectious and parasitic diseases, no. in millions (%)		Infectious diseases burden (%)*
Low- and Middle-Income	5,219	(85)	1.387	(90)	321	(99)	29
High Income	929	(15)	149	(10)	3	(1)	4
Total	6,148	(100)	1,536	(100)	324	(100)	27

*includes respiratory infections
Mathers et al., 2006, in Lopez et al, *Global Burden of Disease and Risk Factors*

Table 2. Disease Burden, Low and Middle Income Countries, by World Bank Region, 2001

Countries	Population in millions (%)		Disability-Adjusted Life Years (DALYs)				
			For all diseases, no. in millions (%)		For infectious and parasitic diseases, no. in millions (%)		Infectious diseases burden in region (%)*
Sub-Saharan Africa	668	(13)	345	(25)	173	(54)	59
South Asia	1.388	(27)	409	(29)	88	(27)	31
Middle East/ North Africa	310	(6)	66	(5)	7	(2)	16
East Asia/Pacific	1.850	(35)	346	(25)	37	(12)	14
Latin America/ Caribbean	526	(10)	104	(8)	10	(3)	13
Europe/Central Asia	477	(9)	117	(8)	5	(2)	6
Total	5.219	(100)	1.387	(100)	320	(100)	29

*includes respiratory infections
Mathers et al., 2006, in Lopez et al, *Global Burden of Disease and Risk Factors*

Communicable diseases

Communicable diseases are responsible for 29 per cent of the burden in LMIC and 27 per cent globally: within Africa and South Asia they comprise 59 per cent and 31 per cent of the total, respectively (Table 2). HIV/AIDS, malaria, pneumonia, diarrhea and peri-natal conditions (asphyxia, trauma, low birth weight and infections) remain the top infectious priorities in Sub-Saharan Africa and South Asia; these diseases affect under-fives disproportionately but for HIV/AIDS where adult illness and mother-to-child transmission are of great importance. Seven infectious diseases comprise 24 per cent of the disease burden in LMICs; Sub-Saharan Africa has the highest burden of HIV/AIDS, malaria, measles, and sexually transmitted diseases (Table 3). Cost-effective treatment and prevention measures are available for many of these conditions.

Table 3. Infectious Burden, Low-and Middle-Income Countries by World Bank Region, 2001

		Disease burden by region, %					
Disease	**Disease Burden in LMICs DALYs,%**	**SSA**	**SA**	**ME/NA**	**EA/P**	**LA/C**	**E/CA**
Respiratory inf.	6.3	3.6	40	4	14	4	3
HIVAIDS	5.1	79	10	1	4	3	1
Diarrhea disease	4.2	37	38	4	15	4	1
Malaria	2.9	89	6	2	3	1	1
TB	2.6	22	38	2	30	3	4
Measles	1.7	59	28	2	10	0	1
STD	0.7	40	39	4	9	5	2
Total	23.5						

SSA = Sub Saharan Africa; SA = South Africa; ME/NA = Middle East/North Africa; EA/P = East Asia/Pacific; LA/C = Latin America/Caribbean; E/CA = Europe/Central Asia
Mathers et al., 2006, in Lopwz et al, *Global Burden of Disease and Risk Factors*

Non-communicable diseases

Cardiovascular diseases (CVD) are the number one cause of death, responsible for 25-to-28 per cent of mortality in all regions except Sub-Saharan Africa (Mathers et al., 2006 and Lopez et al., 2006). The high-

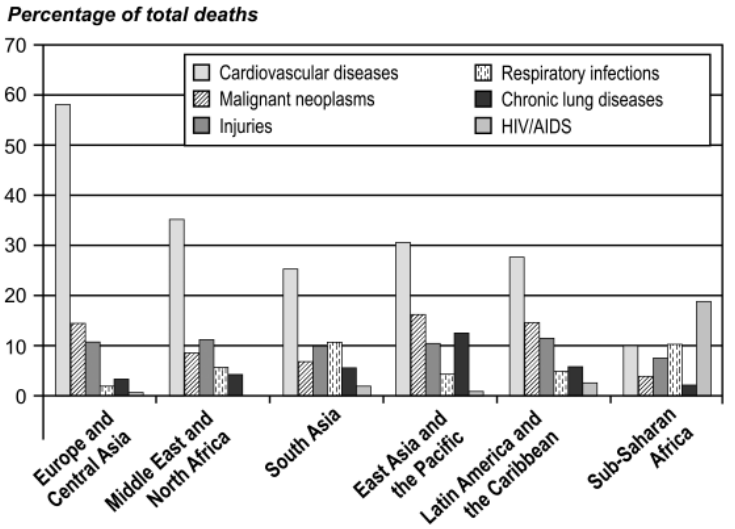

Figure 3. Major Causes of Death in Persons of All Ages in Low- and Middle-Income Regions
Source: Mathers and others 2006

income countries suffer most from CVD, depression, the dementias, and pulmonary system cancers. Noteworthy is that CVD, perinatal conditions, depression, obstructive pulmonary diseases, homicide/violence, suicide, and traffic accidents are in the 'top five' inside four of the six LMIC regions. Ischemic heart disease (IHD), stroke and congestive heart failure (CHF) account for 80 per cent of the CVD burden.

Eighty-two percent of DALYs resulting from IHD occur in LMICs. Most CVD mortality in LMIC is attributable to a few risk factors: high blood pressure, abnormal blood lipids, physical inactivity, overweight, and tobacco use. Being overweight is a major risk factor for diabetes, which also contributes to the burden of CVD. There is no specific low cut-off point for amount of tobacco smoked, blood pressure, cholesterol or body weight as factors for CVD that will assure a decreased risk; thus, there is the attraction of and recommendation for the 'absolute risk factor' approach, aiming to reduce any or all of these risk factors in the population, with benefits depending on the underlying risk.

Table 4. Contributions of Risk Factors to Cardiovascular Disease Mortality Due to Low-and Middle-Income Countries, 2001

	Risk Factor	Ischaemic heart disease (PAF, %)	Stroke (PAF, %)
1.	High blood pressure	47 %	54 %
2.	High cholesstrol	43	12
3.	Low fruit and vegetable intake	27	10
4.	Physical inactivity	20	6
5.	Overweight and obesity	14	7
6.	Smoking	11	8
7.	Alcohol use	4	5
8.	Urban air pollution	4	4
Joint PAF		79	61

PFA - population attributable fraction
M.Ezzati, et al., 2006, in *Global Burden of Disease and Risk Factors*

Table 5. How Much Health will a Million Dollars Buy?

	Service or Intervention	DALYs Averted ($ per DALY)
➢	**Reducing under-5 mortality**	
	• Expanding immunization coverage (EPI diseases)	50,000-500,000 ($2-20)
	• Switch to artemisinin-combination therapy (ACT) where malaria is drug-resistant	50,000-125,000 ($8-20)
	• Improved neonatal care (newborn resuscitation)	2,500-100,000 ($10-400)
	• Adding vaccines to EPI (Hib and hepatitis B)	4,000-24,000 ($40-250)

EPI - Expanding Programme on Immunization
HIb: *Haemophilus influenza, dye b*
Laxminarayan et al., 2006

Interventions

The DCPP has described the effectiveness of 319 interventions in dollars invested per DALY averted (Laxminarayan et al., 2006); 204 are personal and 115 are population-administered. Interventions against the communicable diseases have the most advantageous cost-effectiveness ratios. Table 5 shows how much health a million dollars will buy for reducing under-five mortality for a few advantageous interventions. In general, interventions against communicable diseases are the best buys, and childhood immunization, malaria treatment and prevention, and neonatal care are among the very best buys. Treatment programs with poor adherence to the recommended regimens are not cost-effective as

has been shown with some HIV/AIDS and tuberculosis control programs (Laxminarayan et al., 2006).

A wide range of drugs is effective for treatment of CVD; aspirin for treatment and secondary prevention of stroke, and aspirin plus beta-blockers for treatment and secondary prevention of acute IHD, are the most cost-effective interventions. By far the best approach to the management of CVD is primary prevention, with implementation at the population level of interventions addressing the most common risk factors. The next best approach would be secondary prevention, in which an effective drug regimen is employed by those who have already suffered a cardiovascular insult to reduce the risk of a recurrence. Likewise, cost-effective preventions exist for tobacco and other addictions (taxation), traffic injuries (speed bumps), and undernutrition (micronutrient and food supplementation). DCPP findings show that emergency care and surgical approaches to trauma, obstetrical and other common problems in poor countries are cost-effective. Studies are beginning to demonstrate that treatments of mental illness and diabetes in LMIC can be very cost-effective and respond to a huge, growing, and more increasingly-appreciated burden. Table 6 shows exceedingly advantageous cost-effective interventions for preventing and treating tobacco-induced disease and CVD; the use of more expensive drugs and surgical approaches for IHD are not cost-effective where resources are constrained.

Table 6. How Much Health will a Million Dollars Buy?

Service or Intervention	DALYs Averted ($ per DALY)	
➢ **Preventing and Treating Non-Communicable Disease**		
• Taxation of tobacco products	24,000-330,000	($3-50)
• Treatment of acute myocardial infarction attacks with an inexpensive set of drugs	40,000-100,000	($10-25)
• Treatment of AMI with inexpensive drugs plus streptokinase	1,300-1,600	($3-50)
• Lifelong treatment of heart attack and stroke victims with daily 'polyplill'	1,000-1,400	($700-1,000)
• Coronary artery bypass grafting in specific identification high risk cases	<40	(>$25,000)
• Bypass surgery for less severe coronary artery disease	Very small	(Very high)

AMI - acute myocardial infarction
Laxminarayan et al., 2006

Health systems

DCPP addresses the management and improvement of health care systems by overcoming the inefficiencies in the delivery systems of LMIC. Constraints are shown in Table 7 (Mills et al., 2006 and Travis et al., 2006). Rigorous training and retraining of staff and adherence to high standards of clinical and preventive medicine are essential, as is attention to professional and financial incentives for health care workers, particularly those in rural areas. The constraint levels include: the household and community; the health services delivery infrastructure; health sector policies and management; public policies across sectors; and contextual problems, such as corruption, political stability and the physical environment.

Table 7. Health System Constraints

• Financial inaccessibility (inability to pay fees)
• Physical inaccessibility (distance)
• Unskilled staff
• Unmotivated staff
• Weak planning/management
• Lack of intersectoral actions/partnerships
• Poor quality care in private sector

Mills et al., 2006; Travis et al., 2006 in the *Lancet*

Research and product development

Every intervention was once the object of basic and applied research. The process begins with an understanding of disease mechanisms and determinants, distribution, and predictors of spread. Hence, the research to develop new intervention tools and methods includes studies in cell biology and pathogenesis, immunology, genetics, clinical epidemiology and social sciences.

Advances in vaccine development provide excellent examples of how research benefits health and development. Generally, organisms must be isolated and grown *in vitro*, attenuated or killed and tested as vaccines in animal models and then humans. Responses are tested using immunological surrogates. The recent creative development of human papilloma virus vaccine showed that several of these steps were not essential to produce

an efficacious vaccine product that is now licensed (Mahmoud et al., 2006). What was needed was a large coalition of collaborators in the public and private sectors who developed scientific and business plans focusing on results.

Table 8 indicates the desired results of research: these are new and improved tools and implementation methods. Studies to assure the proper application of effective interventions is 'implementation research' – and this area is of equal or more importance than any other aspect of the scientific enterprise. The dissemination of new knowledge is essential to scientific advancement and the prompt application of new discoveries is essential for economic development.

Table 8. Results of Research and Product Development

New and improved tools
• Drugs
• Vaccines
• Diagnostics
• Devices
• Prostheses and equipment
• Vector control
• Environmental modification
• Behavioral, social, and economic change
New and improved intervention methods
• Treatment algorithms and guidelines
• Intervention packaging
• Costing and cost-effectiveness
• Delivery: health systems and health services
• New and improved policy instruments

The DCPP has several chapters devoted to research and the major conclusions are: research priority setting should focus on the most common problems of LMIC which are, in many cases, also those of high income countries; there must be increased global research training and analytic capability, especially in institutions that are most influential in decision-making; the potential of the information technology revolution needs to be exploited to promote communication and research locally; the 21st century will be one of predictive and preventive medicine and public

health, brought about by advances in molecular genetics, immunology, and better understanding of social sciences and the environmental milieu (Mills et al., 2006 and Mahmoud et al., 2006). A review of research themes identified in DCPP are covered in an upcoming publication (Michaud et al., 2006).

Conclusion

The DCPP has published three books. The analyses used the DALY as the major metric for defining disease burden and cost-effectiveness of personal and population-based health sector interventions as guides for decision makers. The DCPP goals are to stimulate local priority setting planning and programs.

The main DCPP messages are:

1. Average life expectancy in low-and middle-income countries increased dramatically in the past half-century, while cross-country health inequalities decreased.
2. Improved health has contributed significantly to economic welfare.
3. Four critical challenges face developing countries and the world at the dawn of the 21st century. These are:
   - High levels and rapid growth, for mostly demographic reasons, of non-communicable conditions are occurring in developing countries.
   - The HIV/AIDS pandemic is still unchecked in most areas of the world.
   - There is persistence in many countries and many population subgroups of preventable levels of malaria, tuberculosis, diarrhea, pneumonia, and micronutrient malnutrition; and, for mothers and infants, morbidity and mortality associated with childbirth and the neonatal period.
   - There remains the possibility of a successor to the influenza pandemic of 1918 and other new emerging perils.
4. DCPP's conclusions concerning interventions points to a wide range of very good cost-effective buys.

5. DCPP's findings concerning health services include:
   - Increased provision of surgical facilities at the district hospital level are highly attractive.
   - Middle-income countries should consider moving toward public sector financing for health.
6. Continued generation and diffusion of new knowledge and products are key to improvements in health in the 21st century. Future investments are needed in:
   - Research and development.
   - Training leaders in research, operations, and in strengthening healthcare and research institutions.
   - Focusing on LMIC.
7. Future improvements in health and development globally will depend on wide north-south and south-south collaborations, with shared goals and mutual benefits.

Many factors enter into priority-setting and budget allocation. Politics, advocacy, equity, financial and other resources, partnerships, scientific opportunity and national security often drive policy decisions in addition to disease burden and cost-effectiveness of investments. To make rational decisions in resource allocation an analytic capability is required by every government and health ministry to review local data, resources and the benefits of investments to inform policy. As well, research, including implementation research is required to assure a high quality of medical care and to assure the efficacy and effectiveness of new interventions.

Acknowledgments

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References

1. Jamison D.T., Breman J.G., Measham A.R., Alleyne G., et al., Disease Control Priorities in Developing Countries. Second Edition 2006. Oxford University Press and the World Bank, Washington, D.C.
2. Lopez A.D., Mathers C.D., Ezatti M., Jamison D.T., and Murray C.J.L. Global Burden of Disease and Risk Factors. 2006. Oxford University Press and the World Bank, Washington, D.C.
3. Jamison D.T., Breman J.G., Measham A.R., Alleyne G., et al., Priorities in Health. 2006. The World Bank, Washington, D.C.
4. Jamison D.T., Measham A.R., Bobadilla J.L., Mosley W.H. Disease Control Priorities in Developing Countries. 1993. World Bank, Washington, D.C.
5. World Bank. World Development Report: Investing in Health. 1993. World Bank. Washington, D.C.
6. Murray C.J.L., and Lopez A.D., eds. 1996. The Global Burden of Disease, vol. 1. Cambridge, MA: Harvard University Press.
7. Oeppen, J. 1999. 'The Health and Wealth of Nations Since 1820' Paper presented at 1999 Social Science History Conference, Fort Worth, Texas, USA.
8. Mathers C.D., Lopez A.D., and Murray C.J.L. The Burden of Disease and Mortality by Condition: Data, Methods, and Results for 2001 in Lopez A.D., Mathers C.D., Ezatti M., Jamison D.T., and Murray C.J.L. Global Burden of Disease and Risk Factors. 2006. Oxford University Press and the World Bank, Washington, D.C. pp. 45-240.
9. Lopez A.D., Mathers C.D., Ezzati M., Jamison D.T., Murray C.J.L. 'Global and Regional Burden of Disease and Risk Factors, 2001: Systematic Analysis of Population Health Data'. The Lancet, 2006 May 27, 367(9524): 1747-1757.
10. Laxminarayan R., Chow J., and Shahid-Salles S. 'Intervention Cost-Effectiveness: Overview of Main Messages' in Jamison D.T., Breman J.G., Measham A.R., Alleyne G. et al., Disease Control Priorities in Developing Countries, Second Edition. 2006. Page 35. Oxford University Press and the World Bank, Washington, D.C. pp 35-86.
11. Laxminarayan R., Mills A.J., Breman J.G., Measham A.R., Alleyne G.A., et al., 'Advancement of Global Health: Key Messages from the Disease Control Priorities Project' The Lancet 2006; 367:1193-208.
12. Mills A., Rasheed F., and Tollman S. 'Strengthening Health Systems' in Jamison D.T., Breman J.G., Measham A.R., Alleyne G. et al., Disease Control Priorities in Developing Countries, Second Edition. 2006. Oxford University Press and the World Bank, Washington, D.C. pp. 87-102.
13. Travis P., Bennett S., Haines A., Pang T., Bhutta Z., Hyder A., et al., 2004. 'Overcoming Health Systems Constraints to Achieve the Millennium Development Goals'. The Lancet 2006; 364:900-6.
14. Bloom B.R., Michaud C.M., La Montagne J.R. and Simonsen L. 'Priorities for Global Research and Development of Interventions' in Jamison D.T., Breman J.G., Measham A.R., Alleyne G., et al., Disease Control Priorities in Developing Countries, Second Edition. 2006. Oxford University Press and the World Bank, Washington, D.C. pp.103-118.

15. Weatherall D., Greenwood B., Chee H.L., and Wasi P. 'Science and Technology for Disease Control: Past, Present, and Future' in Jamison D.T., Breman J.G., Measham A.R., Alleyne G., et al., Disease Control Priorities in Developing Countries, Second Edition. 2006. Oxford University Press and the World Bank, Washington, D.C. pp. 119-137.
16. Mahmoud A., Danzon P.M., Barton J.H., and Mugerwa R.D. 'Product Development Priorities' in Jamison D.T., Breman J.G., Measham A.R., Alleyne G. et al., Disease Control Priorities in Developing Countries, Second Edition. 2006. Oxford University Press and the World Bank, Washington, D.C. pp. 139-155.
17. Michaud C., Breman J.G., Shahid-Salles S., Maslen P. and Glass, R. A. 'Priorities for Health Research to create New and Improved Interventions: Key Messages from the Disease Control Priorities Project'. Manuscript 2006.
18. Jamison D T. 'Investing in Health' in Jamison D.T., Breman J.G., Measham A.R., Alleyne G., et al., Disease Control Priorities in Developing Countries, Second Edition. 2006. Oxford University Press and the World Bank, Washington, D.C. pp. 3 – 34.

18

A New Age for Life Sciences: Transcriptome Analysis

Yoshihide Hayashizaki

Introduction

Life science is today advancing faster than ever before, and among all new fields genomic science has established itself as a discipline where biological molecules are systematically analyzed regarding to function, without a specific focus on any particular life phenomenon. A typical activity for such research is the activities of the international FANTOM (Functional Annotation of Mouse) consortium (Kawai et al., 2001) that focuses on collecting and annotating cDNA sequences (a stable converted form of mRNAs transcribed from the genome). The heart of FANTOM is the Genome Exploration Research Group located at the Genome Science Center, RIKEN Yokohama Institute.

The efforts of FANTOM and the Human Genome Project (Lander et al., 2001) have given us the first clues to the overall structure and organization of mammalian genomes and transcriptomes. The goal was to understand how genes were expressed and transcribed by having the entire genome sequenced. A large surprise came when we realized that this was not enough in order to understand the complexity of life. Instead of solving the mystery of gene expression, we unraveled a new level of complexity in the transcriptome. The common view before our findings

was based on a DNA-protein world where the DNA carried information, proteins were the biologically active products and the executers of different tasks in the cell and RNA the mediating messenger between them.

Since the beginning of the new millennium, new RNA functions have been discovered at a rapid rate and after the first discovery of double stranded RNA regulation mechanisms, a.k.a. RNA interference (Hannon, 2002), more and more aspects of RNA regulation have been revealed. Non-coding RNA (ncRNA) together with the name of some major groups of ncRNA, short interfering RNA (siRNA) and micro RNA (miRNA), has become a popular science buzzword with over a thousand articles published only in the last year. This trend can also be seen in the number of RNA related patent applications jumping upwards from 2001 (of which more than 80 per cent was filed by industry, showing that the research community is strongly supported by the industry). It has become clear that we have reached yet another phase of research in recognizing the importance of the largely unexplored RNA continent, where we have to reconsider what we know, understand what we are learning and anticipate in which direction this research will take us.

The Mouse Encyclopedia Project and the FANTOM Consortium

In 1995, the Mouse Genome Encyclopedia Project was proposed as a national project, and it begun as one of two genome projects launched by the Ministry of Education, Culture, Sports, Science and Technology of the Japanese Government.

The Mouse Encyclopedia Project concerned the sequencing and analysis of mouse full-length cDNA sequences, while the other project was focused on the contribution to the international human genome sequencing collaboration. At this time, the US NIH (National Institutes of Health) had announced a future time plan regarding the completion of the human genome and the goal was to finish in 2003. It is important to realize that at this time the sequencing of the *Haemophilus influenzae* (a bacterium with a moderately sized genome) genome was just completed as the first free-living organism, and this was seen as a major effort.

Our Mouse Genome Encyclopedia Project complemented the Human Genome Project. The fundamental difference between these projects

(sequencing and full-length cDNA analysis), lies in the fact that while the DNA sequence is the same in all cells, the cDNA project uses the expressed mRNA, which is converted into cDNA before sequencing. The sequencing project thereby gives us one dimension of the genome while cDNA sequencing adds a temporal and an additional quantitative aspect to the data.

To avoid ethical problems involved in using human tissues, and to get the full range of transcripts during development, we chose to use mouse as our model organism and the Mouse Genome Encyclopedia Project was born. The purpose of the project was to create a Mouse Genome Encyclopedia describing cDNA sequences and their properties, such as genomic position, tissue specificity, protein products and protein-protein interactions.

We knew that there was no available technology at that time capable of the large amount of analyses needed. Therefore a secondary goal of the project was the development of a series of novel technologies related to cDNA sequencing. In particular, we developed our own high-speed cDNA sequencing method (Shibata et al., 2000)

Mouse Encyclopedia and FANTOM Technology

Despite the considerable throughput of our technology, it is not realistic to identify all genes experimentally by the use of sequenced full-length cDNA, and the remaining genes are not always possible to find through computational means. In order to obtain these missing full-length cDNA sequences, we developed the Cap Analysis of Gene Expression (CAGE) method (Shiraki et al., 2003). The CAGE method is based on preparation and sequencing of DNA tags deriving from the initial 20 nucleotides in the 5'end of the target mRNA. This technique was combined with two other key technologies Gene Signature Calling (GSC) and Gene Identification Signature (GIS) (Ng et al., 2005), which is based on sequencing tags from the start and the end of the mRNA

The tags from all methods are then sequenced and mapped to the genome to identify transcriptional regions. The combination of CAGE, GIS, GSC and standard full-length cDNA sequencing gives a high-resolution assessment of the transcription landscape in mammalian

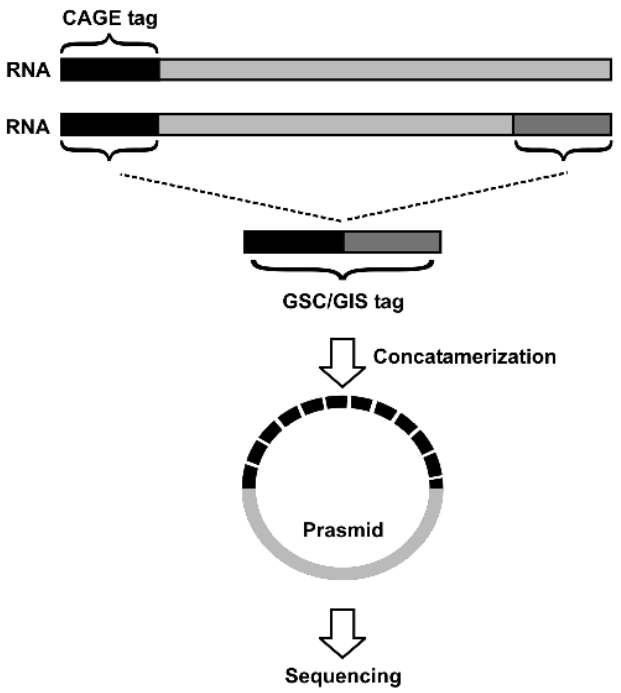

Figure 1. Cage and GSC/GIS

genomes. The FANTOM consortium has managed to collect ~100,000 full-length mouse cDNA clones, ~60,000 human full-length cDNA clones, ~11.6 million mouse CAGE tags, ~11.2 million human CAGE tags and ~2.5 million GSC/GIS tags.

The Discovery of the new RNA Continent

The conclusion of FANTOM revealed that the majority of the entire genome sequence is transcribed contradicting the earlier conception of large transcription 'deserts' where no transcription was believed to take place. This is in sharp contrast to the small fraction (two per cent) (Carninci et al., 2005) of the genome that consists of protein-coding exons: we virtually stand in the middle of a forest of transcripts.

Of these transcripts ~53 per cent (23,218) (Carninci et al., 2005) were found to be non-coding (the final product is not a protein). Only approx.

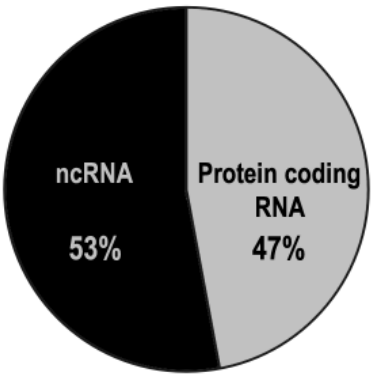

Figure 2. Protein coding RNA and non-coding RNA

100 classic ncRNAs had been reported such as ribosomal RNA (rRNA) and transfer RNA (tRNA), which are involved in protein translation, and small nuclear RNA (snRNA), which is involved in splicing in the nucleus. Other RNAs molecules were earlier believed to be noise, accidental transcription or experimental artifacts. Later RNA interference was discovered, where short RNA sequences, miRNA, are capable of silencing gene expression. Our study showed a multitude of longer ncRNAs as well.

Many of these longer ncRNA are overlapping a protein-coding transcript on the opposite strand, forming an antisense pair. In fact, as much as 72 per cent of all RNA sequences are involved in potential sense/antisense (S/AS) pairs (Katayama et al., 2005). This S/AS pair formation can be a possible way of regulating the final protein product, where the knock-down of an mRNA on the sense strand directly yielded a higher expression of the antisense strand. Many S/AS pairs can be connected to cancer responses and drug metabolism cascades, and the interest for the formation of S/AS pairs as a regulatory mechanism is increasing dramatically in the field of life sciences. We hope in the future to be able to identify these ncRNA and S/AS pair interactions more accurately in order to understand the complexity of the transcriptome, and how disturbances in this network can cause disease. Then we will truly have made a discovery to health.

Functional RNA molecules were previously believed to be the remains of an earlier 'RNA world' (Joyce, 2002). The RNA world is an old concept regarding the origin of life, where RNA was the first organic molecule

being able to independent duplication. According to this hypothesis, RNA was later succeeded by DNA as a static information carrier, and proteins took over the enzymatic and structural functions in the cell. RNA remained only as a messenger and mediator between DNA and proteins.

Today we know that RNA is not merely a mediator, we have RNAi (RNA controlling gene expression by both targeting mRNA transcripts for destruction, slowing translation and by causing methylation to occur in the DNA) (Kim, 2005 Olsen, et al., 1999, Zilberman, et al., 2003), and we know that besides the RNA we already know, tRNA, rRNA and the novel miRNAs etc, there are still unclassified transcripts waiting for analysis. We have an entire hidden world of RNA and RNA functions, interactions and structures that awaits exploration; the RNA continent.

Data Distribution and Distribution Technologies

The FANTOM database consist today of approximate two million clones, first partially sequenced at the 3' and 5 ' ends, then classified and determined to full-length, and manually annotated in the FANTOM Consortium meetings in which more than 100 researchers from 51 research institutes all over the world participated. All together, these efforts have resulted into a database and a clone library setting the gold standard for similar collections and a global biological resource platform for molecular biology studies. On average, every year clones are delivered to 920 laboratories worldwide and the FANTOM database website is counting one visit every five seconds.

As a major distributor of clones we encountered severe shipping problems, where every package huge amounts of dry ice when transporting clones has *Escherichia coli* strains. To solve this transportation problem, we developed the DNABook (Kawai et al., 2003), which today is a complement to the traditional way of sending clones in iceboxes. Simply put, the book consists of pages where cDNA is printed; the cDNA is recovered by dissolving the paper in water. This technique allows us to store and ship the samples at room temperature as an ordinary book. The amount of clones also allows the researcher to try different clones *ad hoc* without having to reorder the material. The first DNABook featured the

mouse transcriptome, followed by books with *Arabidopsis thaliana*, *Oryza sativa* (rice), *Pyroccoccus* (thermo stable bacteria), the human metabolome and fish disease cDNAs.

Conclusions

New technologies drive research forward; at the same time new research ideas require new technology to test ideas. In a close race between research and technology, the FANTOM consortium has not yet reached the finishing line, and we intend to keep our pace high. Life sciences have reached and stepped past several milestones during the last century. We have discovered DNA and managed to sequence the entire genome. Today we discuss personalized genome sequencing for tailor-made medical treatments. RNA was found to exist as ncRNA with a capacity for regulating gene expression, new ncRNA varieties are found all the time; and the hidden RNA world was revealed. Where will our next step take us?

The complexity of human development cannot be explained by our previous picture of the genome, instead it arises from interlocking networks of RNA molecules, regulating the genome expression both in a temporal and a spatial manner.

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References

1. J. Kawai, et al., 2001. Functional annotation of a full-length mouse cDNA collection. Nature 409, 6821. 685-90.
2. E. S. Lander, et al., 2001. Initial sequencing and analysis of the human genome. Nature. 409, 6822. 860-921.
3. G. J. Hannon. 2002. RNA interference. Nature 418, 6894. 244-51.
4. K. Shibata, et al., 2000. RIKEN integrated sequence analysis (RISA) system--384-format sequencing pipeline with 384 multicapillary sequencer. Genome Res. 10, 11. 1757-71.
5. T. Shiraki, et al., 2003. Cap analysis gene expression for high-throughput analysis of transcriptional starting point and identification of promoter usage. Proc Natl Acad Sci. 100, 26. 15776-81.
6. P. Ng, et al., 2005. Gene identification signature (GIS) analysis for transcriptome characterization and genome annotation. Nat Methods. 2, 2. 105-11.
7. P. Carninci, et al., 2005. The transcriptional landscape of the mammalian genome. Science. 309, 5740. 1559-63.
8. S. Katayama, et al., 2005. Antisense transcription in the mammalian transcriptome. Science. 309, 5740. 1564-6.
9. G. F. Joyce. 2002. The antiquity of RNA-based evolution. Nature. 418, 6894. 214-21.
10. V. N. Kim. 2005. Small RNAs: classification, biogenesis, and function. Mol Cells. 19, 1. 1-15.
11. P. H. Olsen, et al., 1999. The lin-4 regulatory RNA controls developmental timing in Caenorhabditis elegans by blocking LIN-14 protein synthesis after the initiation of translation. Dev Biol. 216, 2. 671-80.
12. D. Zilberman, et al., 2003. ARGONAUTE4 control of locus-specific siRNA accumulation and DNA and histone methylation. Science. 299, 5607. 716-9.
13. J. Kawai, et al., 2003. DNA book. Genome Res. 13, 6B. 1488-95.

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Emerging Technologies in Developing-Country Healthcare

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Introduction

Science, technology, and innovation have led to significant progress in the industrialized world; however, this progress has yet to be shared globally. Dramatic improvements in the quality of life of people in industrialized nations have led to life expectancies of 80 years and rising. In striking contrast, millions of people in developing nations continue to struggle with health challenges that no longer affect the developed world, while several African countries face life expectancies of 40 years and falling. Alongside the spread of infectious disease is a rise in chronic non-communicable disease, which continues to hinder development in developing nations, while wealthier countries become better equipped and healthier.

This immense inequity and disparity in global health is perhaps the greatest ethical challenge of our time (Benatar et al., 2003). The Canadian Program on Genomics and Global Health (CPGGH), based at the

University of Toronto has identified three overarching questions to address this challenge:

1. Which emergent technologies are most likely to improve the health of people in developing countries?
2. How can developing countries develop and adopt these technologies for health development?
3. What can industrialized countries do to assist developing countries in harnessing these technologies?

Our goal in addressing these questions is both to strengthen the prospect of emergent technologies such as biotechnology, genomics, nanotechnology, and regenerative medicine in the developing world, and also to emphasize their critical role in global heath.

Emergent Technologies to Improve Health in Developing Countries

In 2000, as part of a commitment to reduce poverty and strengthen sustainable development, all UN member states adopted the Millennium Development Goals (MDGs) and established task forces to help developing countries achieve them. One of these ten task forces focused on Science, Technology and Innovation (Task Force 10), and generated a report titled *Innovation: Applying Knowledge in Development,* stressing the significant role of science, technology and innovation in implementing the MDGs and creating development strategies.

Biotechnology, genomics, nanotechnology, and regenerative medicine have the potential to improve the health of populations in both the developed and developing world, while its applications also have the potential to improve the quality of life and wealth of less industrialized nations (Daar et al., 2002a; Juma and Lee, 2005; UNDP, 2001). UN Secretary General Kofi Annan supports this view and has stated that: "No nation can afford to be without its own [science and technology] capacity." (Annan, 2004).

Genomics

Genomics can be defined as the powerful new wave of health-related life sciences energized by the human genome project and the knowledge and tools it is spawning. Genomics and biotechnology have a tremendous potential to improve global health equity (Singer and Daar, 2001). In 2001 a foresight study entitled *Top 10 Biotechnologies for Improving Health in Developing Countries* was conducted by the CPGGH to identify the biotechnologies that have the greatest potential for improving health in the developing world. Based on the opinions of an international group of eminent scientists, the study identified and prioritized the primary genomic and related technologies required to address health needs in the developing world in an attempt to reduce disparities in global heath.

The three top-ranked biotechnologies were: molecular diagnostics; recombinant vaccines; and vaccine and drug delivery (Daar et al, 2002a). (See Table 1 for a complete listing of the top ten biotechnology applications). As the Genomics and Nanotechnology Working Group of Task Force 10, CPGGH produced a report entitled, *Genomics and Global Health*. The report maps the top ten biotechnologies identified in the foresight study against the MDGs, demonstrating the potential of genomics-related technologies to meet some of these goals, namely: promote gender equality and empower women; reduce child mortality; improve maternal health; combat HIV, malaria and other diseases; and ensure environmental sustainability (Acharya et al., 2004; Daar et al., 2002b). (See Table 2 for a complete list of these goals and the corresponding genomic technology).

Nanotechnology

Nanotechnology can be defined as the study, design, creation, synthesis, manipulation, and application of functional materials, devices, and systems through control of matter at the nanometer scale, that is, at the atomic and molecular levels, and the exploitation of novel phenomena and properties of matter at that scale (Salamanca-Buentello et al., 2005). In 2004, the CPGGH published the results of a survey of nanotechnology activity in developing countries. These results revealed a significant amount of existing activity, which threatens to be derailed by a debate

that fails to take adequate account of developing country perspectives (Court et al., 2004). In 2005, in collaboration with an international panel of experts, we identified and ranked the ten applications of nanotechnology to most likely benefit developing countries in the 2003-2013 period.

The top three rankings were: energy storage, production, and conversion; agricultural productivity enhancement and water treatment and remediation (Salamanca-Buentello et al., 2005). (See Table 1 for the top ten nanotechnology applications). As with the top ten biotechnologies, to further assess the impact of these applications, we mapped the top ten nanotechnologies against the MDGs, demonstrating that the top ten nanotechnologies can have an impact similar to that of biotechnology on sustainable development and a potential to contribute to achieving the MDGs.

Regenerative Medicine

Regenerative medicine is an emerging interdisciplinary field of research and clinical applications focused on the repair, replacement or regeneration of cells, tissues or organs to restore impaired function resulting from any cause, including congenital defects, disease, trauma and aging. By combining several technological approaches, regenerative medicine aims to move beyond traditional transplantation and replacement therapies and address some of the major challenges facing these therapies today, such as organ shortages, graft rejection, and poor graft survival (Greenwood et al., 2006). To date, the field of regenerative medicine has largely focused on the populations of developed countries. It is the case, however, that the conditions that are among the main targets of regenerative medicine, that is non-communicable diseases and injuries and trauma, occur at higher rates in the developing than developed world (WHO, 2005).

We conducted a foresight study with an international panel of experts to identify the ten most promising applications of regenerative medicine for improving health in developing countries. The top-three applications identified by the expert panel were: novel methods of insulin replacement and pancreatic islet cell regeneration for diabetes; autologous cells for the regeneration of heart muscle after myocardial infarction and cardiomyopathies; and immune system enhancement by

Table 1. Top 10s: Biotechnologies, Applications of Nanotechnology and Regenerative Medicine Applications for Improving Health in Developing Countries

Top 10 biotechnologies for improving health in developing countries	
1	Modified molecular technologies for affordable, simple diagnosis of infectious diseases
2	Recombinant technologies to develop vaccines against infectious diseases
3	Technologies for more efficient drug and vaccine delivery systems
4	Technologies for environmental improvement (sanitation, clean water, bioremediation)
5	Sequencing pathogen genomes to understand their biology and to identify new antimicrobials
6	Female-controlled protection against sexually transmitted diseases, both with and without contraceptive effect
7	Bioinformatics to identify drug targets and to examine pathogen-host interactions
8	Genetically modified crops with increased nutrients to counter specific deficiencies
9	Recombinant technology to make therapeutic products (e.g. Insulin, interferons) more affordable
10	Combinatorial chemistry for drug discovery

Top 10 applications of nanotechnology for improving health in developing countries	
1	Energy storage, production and conversion
2	Agricultural productivity enhancement
3	Water treatment and remediation
4	Disease diagnosis and screening
5	Drug delivery systems
6	Food processing and storage
7	Air pollution and remediation
8	Construction
9	Health monitoring
10	Vector and pest detection and control

Top 10 regenerative medicine applications for improving health in developing countries	
1	Novel methods of insulin replacement and pancreatic islet cell regeneration for diabetes
2	Autologous cells for the regeneration of heart muscle after myocardial infarction and cardiomyopathies
3	Immune system enhancement by engineered immune cells and novel vaccination strategies for infectious disease
4	Tissue engineered skin substitutes, autologous stem or progenitor cells, intelligent dressings, and other technologies for skin loss due to burns, wounds, and diabetic ulcers
5	Biocompatible blood substitutes for transfusion requirements
6	Umbilical cord blood banking for future cell replacement therapies and other applications
7	Tissue engineered cartilage, modified chondrocytes, and other tissue engineering technologies for traumatic and degenerative joint disease
8	Gene therapy and stem cell transplants for inherited blood disorders such as thalassemias, sickle cell disease, and hemophilia
9	Nerve regeneration technologies using growth factors, stem cells, and synthetic nerve guides for spinal cord and peripheral nerve injuries
10	Hepatocyte transplants as replacement therapy for chronic liver diseases or liver failure

engineered immune cells and novel vaccination strategies for infectious disease (Greenwood et al., in press) (See Table 1 for a complete list). In addition, we conducted a preliminary Internet-based survey to identify regenerative medicine activities already underway in 31 low- and middle-income countries and emphasized that although regenerative medicine is still an emerging field; developing countries are already actively engaging in its pursuit (Greenwood et al., 2006).

Adopting New Technologies for Health Development

The CPGGH *Genomics and Global Health* report identified the importance of having developing countries as key actors in using biotechnology and genomic-based technologies to address local health needs. We conducted a 3-year empirical case study of the health biotechnology innovation systems in seven developing countries that have developed capacity in the health biotechnology sector, namely: Brazil, China, Cuba, Egypt, India, South Africa, and South Korea. Results were published in a *Nature Biotechnology* supplement titled, *Health Biotechnology Innovation in Developing Countries* (Thorsteinsdottir et al., 2004). Through detailed analysis, we identified lessons learnt and key factors derived from success stories that may help other developing countries embark on fostering their own indigenous health biotechnology sector (see Table 3 for a listing of major findings).

Each of the case studies emphasized the *importance of political will* in establishing and promoting health biotechnology innovation in developing countries. In order to promote the growth of health biotechnology, governments have developed specific policies that recognize the importance of the research, and elaborated ways of responding to the ongoing challenge of brain drain, by increasing funding for scientific research, and by providing biotechnology enterprises with incentives to overcome difficult economic conditions. A common theme in the case studies was that a few individuals have played important leadership roles and have been instrumental in encouraging health biotechnology development in their countries. Defining niche areas, such as preventative vaccines, was identified as another key factor in establishing a successful health biotechnology sector, given the limited resources for technological development in less industrialized countries. Close linkages of research,

Table 2. Genomics and Related Technologies Can Support the MDGs.

MDG	Statistics/Facts	Biotechnology to Address MDG
Goal 3: Promote gender equality and empower women	In 2001, 57 per cent of HIV cases in sub-Saharan Africa were women. Average HIV infection rates in teenage girls are five times higher than those in teenage boys	• Female control over STD transmission protection • Vaccine and drug delivery
Goal 4: Reduce child mortality	About 11 million children die Before reaching their fifth birthday	• Molecular diagnostics • Vaccine and drug delivery • Recombinant vaccines • Female control over STD transmission protection • Nutritionally enriched GM crops • Combinatorial chemistry
Goal 5: Improve maternal health	Over 500,000 maternal deaths per year	• Molecular diagnostics • Vaccine and drug delivery • Recombinant vaccines • Female control over STD transmission protection • Nutritionally enriched GM crops • Combinatorial chemistry
Goal 6: Combat HIV, malaria, and other diseases	HIV/AIDS, malaria, and tuberculosis are responsible for more than six million deaths worldwide	• Molecular diagnostics • Vaccine and drug delivery • Recombinant vaccines • Female control over STD transmission protection • Bioremediation (using living organisms to degrade/ transform hazardous organic contaminants) • Sequencing pathogen genomes • Bioinformatics • Enriched GM crops • Combinatorial chemistry
Goal 7: Ensure environmental sustainability	five million deaths per year can be attributed to waterborne diseases	• Bioremediation

Source: Acharya, T., Daar, A.S., Dowdeswell, E., and Singer, P.A., Thorsteinsdóttir, H. 2004. Genomics and Global Health: A report of the genomics working group of the Science and Technology Task Force of the UN Millennium Project. University of Toronto Joint Centre for Bioethics, Toronto, Canada.

business, policy, health institutions and other actors in the field ensure active knowledge flows, which are essential for innovation to take place.

One important factor we identified was the focus on the use of biotechnology to meet local health needs. South Africa has prioritized research on HIV/AIDS, its largest health burden, and developments are underway for a vaccine against the strain most prevalent in the country; Egypt is responding to its need to address diabetes locally by focusing its research and development efforts on locally producing recombinant insulin; and Cuba developed the world's only meningitis-B vaccine as a response to a national outbreak. Other factors include the notion that there is no one-size-fits-all solution when it comes to succeeding in health biotechnology innovation, and the fact that basic education and health systems are important building blocks for health biotechnology development.

A key finding of the report was the important role that domestic private sector firms in developing countries can play in developing health products that are targeted to the specific health needs of local populations. Likewise, The UN Commission on Private Sector and Development has also recently emphasized the role of the domestic private sector in the development of developing countries. In the 2004 report *Unleashing Entrepreneurship, Making Business Work for the Poor* the Commission argued that the managerial, organizational and technological innovation that resides in the private sector, particularly the small and medium enterprise segment, can improve the lives of the poor by empowering citizens and contributing to economic growth.

We recently initiated a study to examine how the domestic health biotechnology sectors of four developing countries -- India, China, Brazil and South Africa -- contribute to addressing local health needs. The purpose of the study is to understand better how developing country firms prioritize the development of health products geared towards addressing local health needs, their capabilities and capacities for developing such products, and the barriers, incentives and financing available for doing so, including the availability of both publicly and privately offered funds. Preliminary findings regarding India's health biotechnology sector indicate a number of promising success stories that demonstrate how this country's homegrown health biotechnology sector is addressing local and global health needs (Frew et al., 2006). Together, this research can be used

to provide heads of state and science ministers in developing countries with specific guidance and good practices for implementing innovation policies that utilize the strengths of both the public and private sectors in developing and implementing health technology to address local health needs.

It is worth noting that the countries studied are those that are scientifically advanced and all have placed emphasis on health innovation (Mashelkar, 2005; Morel et al, 2005). The hope is that the lessons we identify in these countries can be applicable in countries with limited scientific capacity. There are clear signs that there is a growing divide between developing countries and counties that have significantly promoted scientific development are surging ahead of other developing countries. We are just starting a research project examining south-to-south collaboration between developing countries in order to identify ways to bridge this divide and extend capacity building and innovation in countries with limited scientific capacity.

A Role for Industrialized Countries

In January 2003, the Gates Foundation launched The Grand Challenges in Global Health (GCGH) initiative in partnership with the US National Institutes of Health. The medical research initiative encourages the application of science and technology to the greatest health problems that disproportionately affect the developing world (Varmus et al., 2003). Fourteen Grand Challenges were identified using the expertise of over 1,000 scientists and health experts around the world, including scientific board participation from our group. Since then, 43 research projects involving cutting-edge research have been initiated across disciplines and in collaboration with researchers from both the developing world and private industry. While the GCGH primarily focused on infectious diseases, the CPGGH is also currently working with the Oxford Health Alliance to identify the Grand Challenges in Chronic Non-communicable Disease.

The aim of the GCGH initiative is to create health tools that are effective, inexpensive to produce, easy to distribute and easy to use in developing countries. Likewise, our *Genomics and Global Health* report encourages and emphasizes the creation of a Global Genomics Initiative

(GGI), a global networked initiative that could share and promote the health and environmental benefits being created through genomics-related technologies worldwide. This would potentially contribute significantly to improving health and development outcomes in less industrialized countries.With strong representation from the developing world in a partnership between industry leaders, citizens, academics, non-governmental organizations and government officials, the network could serve as a governance mechanism at the global level to ensure the effective application of genomics to worldwide challenges (Acharya et al., 2004).

The formation of a GGI could also promote partnerships between industrialized countries and the developing world from both a research and private sector perspective. We are currently examining Canadian collaboration in health biotechnology with developing countries. We are mapping the linkages in health biotechnology and are carrying out case study research on existing collaboration projects to determine how collaborations can be strengthened and leveraged to have a greater impact on addressing the health needs of developing countries and increasing opportunities for Canadian biotechnology firms to internationalize in emerging markets. This project builds on a previous study in which we interviewed decision-makers in biotechnology companies throughout Canada in order to determine the market failures that inhibited them from both identifying and pursuing opportunities in developing and emerging market economies and ways in which to overcome these barriers. Specific areas in which the government could provide enhanced services to enable the development of emerging market opportunities were also identified.

The importance of the role of human capital in a global economy cannot be underestimated and for developing countries, the migration of skilled professionals to developed countries has significant social and economic consequences. Policies that encourage utilizing the resources (human and capital) of diasporas without permanently repatriating them to their home countries promotes the concept of brain circulation. The role that diasporas play in the global economy has been highlighted by the UN Task Force on Science, Technology and Innovation. We have recently suggested that developed countries should make the diaspora option a key component of their international development policy (Séguin et al., 2006a). However, there is very little empirical data on which to base such policy.

In an effort to fill the knowledge gap on how scientific diasporas can make significant contributions toward development beyond remittances, we completed a year-long study of 60 life scientists from 27 developing countries in which participants were asked open-ended questions regarding their views and experiences with respect to contributing to development and innovation (skills, networking, training, management and/or investments) in their home countries and developing countries generally.

The study, published in *Science* (Séguin et al., 2006b), showed that participants had a strong desire to contribute to S&T innovation and development in their home countries. However, most were not involved in any such activities. We emphasize that scientific diasporas are an untapped resource for both the country of origin and their host countries. Findings have led us to suggest a number of policy options that are being submitted to the federal government of Canada for consideration. Both developed and developing countries would greatly benefit by offering incentives and well crafted programmes that engage skilled diasporas. Phase-two of this study will examine how developing countries with diaspora populations in Canada can respond to the needs identified in this study.

We have emphasized biodevelopment as a priority for development; however in lieu of recent events, concerns regarding biosecurity have gained light. There is a risk that attempts to increase biosecurity and prevent bioterrorism could sideswipe legitimate uses of biotechnologies to improve global health. To address this challenge the CPGGH drew on the expertise of a group of international experts to explore ways to reconcile the potentially conflicting agendas of biotechnology for development and biosecurity and align the agendas so they become synergistic. We released a report entitled, *DNA For Peace,* which made a number of key recommendations to include:

1. The world must not let legitimate concerns about biosecurity undermine the promotion and use of biotechnologies for human development;
2. We need to invest in positive applications of biological sciences in the developing world in order to protect against the misuse of these sciences for harmful purposes;
3. We recommend a model of global governance that will achieve a balance between the potentially competing agendas of biosecurity and biodevelopment consisting of a network of experts, leaders and citizens from around the world; and,

4. To catalyze action the G8 should begin the process of identifying an appropriate organization to serve as host for this initiative (Daar et al., 2006).

In accordance to these recommendations we emphasize the potential of biotechnology to development and stress the important role of ensuring that biodevelopment takes priority.

Conclusion

This paper shows that biotechnology, genomics, nanotechnology, and regenerative medicine have the potential to improve the health of the more than five billion people in the developing world. These cutting-edge technologies will not solve all the predicaments against which developing countries struggle every day such as; problems of conflict, corruption, governance and unfair trade subsidies, which seem ingrained in human nature. However, without science and technology innovation, no country can attain a decent quality of life. With the dedication and commitment from players such as governments, international development and global health institutions, and private firms worldwide, science and technology can be harnessed to minimize the growing divide in global health between the developed and the developing worlds.

Table 3. Core Lessons on Cultivating Health Biotechnology Innovation

Lessons
• Strong and Sustained Political Will
• Individual Leadership
• Close Linkages and Active Knowledge Flow
• Focused Efforts on Particular Niche Areas
• Temporarily Permissive IP Environment Facilitates Initial Capacity Building
• Private Sector Development

References

1. Acharya, T., Daar, A.S., Dowdeswell, E., and Singer, P.A., Thorsteinsdóttir, H. 2004. Genomics and Global Health: A Report of the Genomics Working Group of the Science and Technology Task Force of the UN Millennium Project. University of Toronto Joint Centre for Bioethics, Toronto, Canada.
2. Acharya, T., Daar, A.S., Thorsteinsdóttir, H., Dowdeswell, E., and Singer, P.A. 2004. Strengthening the Role of Genomics in Global Health. PLoS Medicine. Vol. 1, No.3, E40.
3. Annan, K. 2004. 'Science For All Nations'. *Science*. vol 303, No. 925.
4. Benatar, S.R., Daar, A.S., and Singer, P.A. 2003. Global health ethics: the rationale for mutual caring. International Affairs. Vol. 79, pp.107-38.
5. Court, E., Daar, A.S., Martin, E., Acharya, T., and Singer, P.A., 'Will Prince Charles Diminish the Opportunities of Developing Countries in Nanotechnology?' Nanotechweb.Org, January 28, 2004.
6. Daar, A.S., et al., 2002. Top-10 Biotechnologies for Improving Health in Developing Countries, Nature Genetics, Vol. 32, pp. 229-232.
7. Daar, A.S., Martin, D.K., Nast, S., Smith, A.C., and Singer, P.A., Thorsteinsdóttir H. 2002. Top 10 Biotechnologies for Improving Health in Developing Countries. University of Toronto Joint Centre for Bioethics, Toronto, Canada.
8. Daar, A.S., Dowdeswell, E., Panjwani, D., Persad, D.L., and Singer P.A. 2006. 'The Global Bargain for Biosecurity', Workshop at the New York Academy of Sciences entitled: 'DNA for Peace: Reconciling Biodevelopment and Biosecurity.'
9. Frew, S.E., Sammut, S.M., Siu, W.W., Daar, A.S. and Singer, P.A. 2006. 'The Role of the Domestic Private Sector in Developing Countries for Addressing Local Health Needs', International Journal of Biotechnology, Vol. 8, Nos. 1/2, pp. 91-102.
10. Greenwood, H.L., Thorsteinsdottir, H., Perry, G., Renihan, J., Singer, P.A. and Daar A.S. 2006. 'Regenerative Medicine: New Opportunities for Developing Countries'. International Journal Biotechnology, Vol. 8, Nos. 1/2, pp. 60-77.
11. Greenwood, H.L., Singer, P.A., Downey, G.P., Martin, D.K., Thorsteinsdottir, H., and Daar A.S. [in press]. 'Regenerative Medicine and the Developing World'. PLoS Medicine.
12. Juma, C., and Lee Y-C. 2005. Innovation: Applying Knowledge in Development. UN Millennium Project: Task Force on Science, Technology and Innovation. London, Sterling Va., pp. 1-220.
13. Mashelkar, R.A., Nation Building through Science & Technology: A Developing World Perspective. 10th Zuckerman Lecture, Royal Society, London.
14. Morel, C.M, Acharya, T., et al., 2005. 'Health Innovation Networks to Help Developing Countries Address Neglected Diseases'. *Science*, Vol. 309, No. 5733, pp. 401-404.
15. Salamanca-Buentello, F., Persad, D.L., Court, E.B., Martin, D.K., Daar, A.S., and Singer P.A. 2005. 'Nanotechnology and the Developing World'. PLoS Medicine. Vol. 2, No.5., E97.
16. Séguin, B., Singer, P., and Daar, A.S. 2006. 'Scientific Diasporas'. Science Vol. 312, pp. 1602-1603.

17. Séguin, B., State, L., Singer, P.A. and Daar, A.S. 2006. 'Scientific Diasporas as an Option for Brain Drain: Re-Circulating Knowledge for Development', International Journal of Biotechnology, Vol. 8, Nos. 1/2, pp.78-90.
18. Singer, P.A. and Daar, A.S. 2001. 'Harnessing Genomics and Biotechnology to Improve Global Health Equity'. Science. Vol.294, pp. 87-89.
19. Thorsteinsdottir, H., Quach, U., Daar, A.S. and Singer, P.A. 2004. 'Health Biotechnology Innovation in Developing Countries', Nature Biotechnology. Vol. 22, DC 3-DC7.
20. UNDP. 2001. Human Development Report: Making New Technologies Work for Human Development, New York: UN Development Program.
21. Varmus, H., Klausner, R., Zerhouni, E., Acharya, T., Daar, A.S. and Singer, P.A. 2003. 'Grand Challenges in Global Health'. Science. Vol. 302, pp.398-399.
22. WHO. 2005. Preventing Chronic Diseases: A Vital Investment: WHO Global Report. WHO, Geneva, Switzerland.

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Innovative Pathways to a Healthier World

Magid Abou-Gharbia

Introduction

Drug discovery and development is a challenging and complex process that involves the dedicated multidisciplinary efforts of many R&D functions. It is becoming increasingly more expensive to carry out innovative drug discovery, and fewer novel therapeutics are making it to market. This story is seemingly the same across industry. Many research organizations have adopted several approaches to ensuring their survival and success in the 21st century by building a robust pipeline that promises to provide significant benefit to patients and caregivers in the coming years. The Discovery Research Group at Wyeth has placed annually 12 new compounds into development since 2001. This was achieved by stepping up our internal R&D activities, putting in place key enabling technologies such as Transcriptional Profiling, High Throughput Screening (HTS), and Translational Research Capabilities. Success has also been achieved by bringing in in-licensed products, engaging in and through collaborations with several academic and industrial partners, and establishing research partnership initiatives and consortia in the US, Europe and Asia.

Drug Discovery and Development

Innovative therapeutics are being produced utilizing three key pharmaceutical platforms: small molecules, proteins and vaccines. Most multinational drug companies use one or two such platforms; only a few of the larger pharmaceutical companies are producing innovative medicine using all three. Over 80 per cent of currently-marketed drugs are based on small molecules; the rest use proteins and vaccines platforms. Small molecules have historically been the driver of the pharmaceutical industry. Drugs based on small molecules include top-selling drugs such as Lipitor™, a lipid-lowering agent; Plavix™, an anti-thrombotic drug; Effexor®XR, an anti-depressant drug and many others (Figure 1).

Drug	Generic Name	Indication	Company
Lipitor™	Atorvastatin	Hyperlipidemia	Pfizer
Zocor™	Simvastatin	Hyperlidipemia	Merck & Co.
Zyprexa™	Olanzapine	Schizophrenia	Eli Lily
Norvasc™	Amlodipine	Hypertension	Pfizer
Prevacid™	Lasoprazole	GERD	Takeda
Nexium™	Esomeprazole	GERD	AstraZeneca
Plavix™	Clopidogrel	Thrombosis	BMS
Seretide™	Salmeterol	Asthma	GSK
Zoloft™	Sertraline	Depression	Pfizer
Celebrex™	Celecoxib	Arthritis pain	Pfizer
Effexor™	Venlafaxine	Depression	Wyeth
Epogen™	Epoetin alpha	Anemia	Amgen
Seroxat™	Paroxetine	Depression	GSK
Risperdal™	Risperidone	Schizophrenia	J&J
Pravachol™	Pravastatin	Hyperlipidemia	BMS
Losec™	Omeprazole	GERD	AstraZeneca
Neurontin™	Gabapentin	Epilepsy	Pfizer
Fosamax™	Alendronate	Osteoporosis	Merck & Co.

Figure 1. Today's Leading Drugs & Major Indications

Drug discovery and development is a challenging and complex process that involves the dedicated multi-disciplinary efforts of many R&D functions. According to recent reports, developing a new drug can take up to 15 years and costs anything between $800 million and $1.7 billion, particularly for innovative biotechnology therapeutics. Fewer than 10 per cent of drug candidates entering Phase I clinical trials will reach the market.

The R&D process starts with discovering activities in disease targets responsible for any given disease or disorder, such as enzymes, proteins and other biomolecules that are identified. This is followed by a process to select chemical molecules that modulate the target. This process involves screening large numbers of compounds against the target.

Company compound banks, typically ranging from 300,000 to 1,000,000 compounds, are used to define the specific types of molecules that will interact with defined targets. As companies have increased the size of their compound banks in order to increase the amount of chemical space covered by the collection and, thus, increase the chance of obtaining a biological interaction, there has evolved a need for sophisticated robotic equipment to screen each of the hundreds of thousands of compounds against the target of interest. This need has led to the emergence of automated screening technology of high throughput screening (HTS), and more recently of ultra-high throughput screening (UHTS).

Compounds having an effect on the target are termed 'hits' and they represent the building blocks for subsequent medicinal chemistry manipulation. The identified leads then undergo what is referred to as lead optimization where both biological activity and physico-chemical properties of the molecules are optimized. The optimized drug candidate enters into the clinical development phase to assess drug candidate safety and efficacy in patients. Drug candidates must meet the specifications set forth by regulators such as the Food and Drug Administration in the US (FDA). It takes screening of over one-million compounds to result in a mere handful of drug candidates in clinical development to produce one marketed drug (Figure 2).

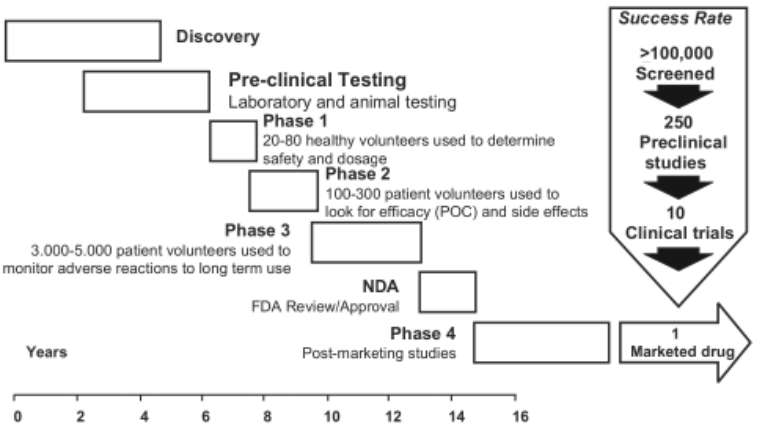

Figure 2. Drug Discovery & Development

Process

Throughout the years, many tools and new technologies have been employed to add quality, increase the R&D success rate and reduce overall cycle time using the technologies of genomics, HTS, structure-based design, parallel synthesis and many others.

A New Generation of Anti-Depressive Therapies

Over the past several decades, depression has changed from being viewed as an episodic disease brought on by a specific stressful incident to a life-long disease with multiple causes both genetic and environmental. The advance in the perception of depression is due mostly to immense scientific studies that have revealed depression as a serious disease combined with an overwhelming increase in the number of cases.

Depression is a whole-body illness with a broad range of physical and emotional symptoms from mood swings, social withdrawal, fatigue, dizziness and a myriad of others. Depression is more prevalent among women with a 2:1 ratio of incidents women to men. Indeed, depression-associated suicide is now the eighth leading cause of death in the US today, surpassing HIV infection; and in the next century depression is predicted to become the leading cause of morbidity.

Depression is usually associated with lower levels of serotonin and norepinephrine in the synaptic cleft. In the mid-1980s it was hypothesized that an effective treatment for depression would be to selectively block the pre-synaptic uptake of not only serotonin, but also norepinephrine. After years of pre-clinical and clinical research and development, Venlafaxine was synthesized and found to have effective anti-depressant activity. It was submitted to the FDA and subsequently approved as an anti-depressive treatment in 1994, Effexor™, and the extended release version, Effexor®XR, was marketed in 1997 as the first SNRI (serotonin norepinephrine reuptake inhibitor) anti-depressant drug and is the most prescribed anti-depressant therapy available today.

Effexor is well tolerated and effective over a wide range of patients; more than 10-million have benefited from Effexor®XR during the last ten years. As the search continues for more effective anti-depressant therapies, a venlafaxine metabolite has been identified as a potent anti-depressant in its own right, but associated with fewer side effects. This compound is currently in registration and is anticipated to be marketed and available to patients in 2007.

A New Generation of Immunosuppressants and Anti-Cancer Agents

Rapamycin is a novel immunosuppressant natural product with unique mechanisms of action. 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. Rapamune® prolongs graft survival and minimizes the risk of developing skin cancer which many transplant patients develop as a result of their compromised immune systems. Semi-synthetic manipulation of Rapamycin led to the synthesis of several novel rapamycin derivatives; over 700 were synthesized and evaluated for their potential biological activity. The hindered ester (Cell Cycle Inhibitor, CCI-779, Torisel™) was selected and subjected to further preclinical and clinical evaluations; it is currently in late Phase III as an anti-cancer agent with anticipated NDA was submitted on October 5th , 2006.

Innovation and Healthcare Access

Despite advances and breakthroughs in healthcare, when it comes to the topic of the pharmaceutical industry and the ongoing efforts by multinationals, developing countries see a clear division for the world market of pharmaceuticals with products being developed for industrialized western countries driven by a high-profit margin; whereas developing countries are still in dire need for basic healthcare.

The reality is that pharmaceutical industry multinationals are a research-based enterprise with a 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 industrialized western world but are 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 governments of developing world countries and health organizations such as WHO and other aid organizations. This includes donating assistance, medicines, and 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. Among these initiatives: The AstraZeneca Research Center in Aviskar, India dedicated to tropical diseases research; Pfizer's efforts in collaboration with academic alliance for AIDS care in Uganda, providing care for HIV-infected patients where over ~400 physicians completed and training; and Wyeth's collaboration with WHO in the battle against Onchocerciasis (eye tumors and frequently blindness) where Wyeth provided unlimited supplies of Moxidectin for Phase III clinical trials as a cure for this devastating disease. These are just a few examples of many such initiatives aimed at helping patients in the developing countries.

References

1. Ashton, M.J., Jaye, M.C. and Mason, J.S. (1996a) New perspectives in lead generation I: Discovery of biological targets. Drug Discovery Today 1:11-15.
2. Ashton, M.J., Jaye, M.C. and Mason, J.S. (1996b) New perspectives in Lead Generation I: Discovery of Biological Targets. Drug Discovery Today 1:71-78.
3. Bernardelli, P., Gaudillière, B., and Vergne, F. (2002) Trends and perspectives: To market. In: Doherty, A.M. (ed), Annual Reports in Medicinal Chemistry Volume 37. Academic Press, San Diego, pp. 257-277.
4. Gibbons Jr., J.J., Discafani, C., Petersen, R. R. Hernandez, R., J. Skotnicki, J. and Frost, P. (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.
5. Molnar-Kimber, K.L. (1996) Mechanism of Action of Rapamycin (Sirolimus, Rapamune). Transplantation Proceedings 28: 964-969.
6. Sehgal, S.N., Molnar-Kimber, K. Ocain, T.D., and Weichman, B.M. (1994) Rapamycin: A Novel Immunosuppressive Macrolide. Medicinal Research Reviews 14: 1-22.
7. Skotnicki, J.S., Leone, C.L., Smith, A. L., Palmer, Y.L., Yu, K., Discafani, C.M., Gibbons Jr., J.J., Frost, P., Abou-Gharbia, M.A. (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.
8. Schechter, Lee E., et al., (2005) Innovative Approaches for Development of Antidepressant Drugs: Current and Future Strategy, NeuroRx, 2, 590-611.
9. Yardley, P.J., Husbands, G.E.M., Stack, G., Butch, J., Bicksler, J., Moyer, J.A., Muth, E.A., Andree, T., Fletcher III, H., James, M.N.G. and Sielecki, A. R. (1990) 2-Phenyl-2-(1-hyroxycycloalkyl) ethylamine derivatives: Synthesis and antidepressant activity. Journal of Medicinal Chemistry 33:2899-2905.

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North-South Collaborations in Digital Molecular Medicine

Rafael Rangel-Aldao

Introduction

In the developing world including those countries of higher income, it is still a necessity to exploit for their benefit major technological advances such as biotechnology, genomics, proteomics, and molecular medicine (Rangel-Aldao, 2004). The main reason appears to be the lack of system integration at all levels of the value chain of health care (Rangel-Aldao, 2005). Another difficulty resides in the lack of effective connectivity of academic institutions with private companies, scientists and entrepreneurs, laboratories and manufacturing facilities. Add to this a weakened framework of intellectual property of inventions and innovations.

In the meantime, a revolution is occurring in biology with a phenomenal impact into medicine signaled by how to manage and exploit the enormous complexity of informational networks to develop better medical care accessed by all. The understanding of cell informational networks is giving rise to the prevention and individualized treatment of major causes of morbidity world-wide such as cancer, type 2 diabetes, cardiovascular, and respiratory disease, among others. It is also possible to conduct large scale epidemiological studies to reveal risk exposure to such ailments by so called single nucleotide polymorphisms, SNPS (Melton, 2003) or by

the expression of key regulatory genes, with techniques such as combined DNA arrays and reverse transcriptase-polymerase chain reaction, RT-PCR (Ramsawamy, 2004). The mission is to bring down escalating costs of health care by targeted campaigns of prevention, and individualized treatment.

The science supporting all this progress is also experiencing profound changes with the fusion of biology to other branches such as mathematics, physics, chemistry, and technologies like biotechnology, nanotechnology, computing and communication (Burrill, 2005). On top of this, biotechnology is becoming commoditized by the ever-decreasing costs of DNA sequencing approaching the $1,000 genome (Service, 2006), as well as the ready availability of contractual research for genomics and proteomics. It is therefore no longer a competitive advantage for any developing nation to establish infrastructure for these types of biotechnologies. Incidentally, such technologies may also become inadequate to understand how the genome interacts downstream with the proteome and metabolome and have a dynamic vision of the whole, or physiome. Reductionism and determinism are thus being complemented with a systems approach occurring throughout the full spectrum of scientific knowledge and business today.

Systems biology is, then, taking root as an integrating tool to comprehend how the genome and proteome respond to environmental changes through the signal transduction machinery of the cell. These fields of research also represent a new avenue for innovation within health systems worldwide and, surprisingly enough, this is where trained scientists and physicians on a global scale, including lower-income countries, could take advantage of the emerging plethora of biomedical knowledge related to the very roots of molecular medicine (Rangel-Aldao, 2003).

The way research is conducted is also changing, to the point that even teams based in a single institution have become insufficient to compete with networks of researchers worldwide. It is therefore necessary to establish links of skilled labour from the South with their counterparts constituting the hubs that coordinate the global networks of knowledge and technology from the North.

Digital Molecular Medicine as an Integrating Tool

All information in biological systems appears to be organized into so-called scale-free networks (Barabasi, 2000). The same topology and 'network motifs' are thus found in a wide range of network interactions of complex mechanisms from ecological systems, neuronal synapses, and electric circuits, to the Internet, among others (Milo et al., 2002). The genome (Luscombe, et al., 2002), proteome (Koonin et al., 2002), metabolome (Jeong et al., 2000), and the physiome (Buchman, 2002) all obey a power-law distribution of nodes and links, typical of scale-free networks, that is, very few nodes such as genes and proteins from these networks exert as hubs the overall control of the entire system, making its complexity amenable to study and practical applications. Such biological networks of information could be represented in digital form as dynamic maps, similar to those of motor vehicle traffic where it is possible to locate possible jams at key junctions or hubs, and from such dynamics establish its physiological consequences to predict risk or the onset of disease. These maps would also reflect the social life of key informational molecules that through their interactions govern vast arrays of physiological responses that when go astray produce disease. For instance, the course of the major causes of morbidity listed above all follow a similar overall pattern that goes from the endoplasmic reticulum, ER, stress to inflammation, and from there on to disease depending on the pathophysiological context.

We have called these few genes and proteins the 'usual suspects' since most of them are always associated with disease although with different partners and combinations. For instance, one single gene, CREBH, a transcription factor, has a major role in the path from ER stress to the acute inflammatory response since upon activation by specific proteases in the lumen of the endoplasmic reticulum, it migrates to the nucleus to activate the genes of C-reactive Protein, CRP, and serum amyloid P-component, SAP, in the liver, two early markers of inflammation (Zhang et al., 2006). Another gene, of the PPAR family, a nuclear receptor and transcription factor, is capable of controlling the expression of a host of genes of lipid homeostasis and exert pleiotropic effects as well on inflammation and cell proliferation to prevent atherogenesis, cardiovascular disease, and the metabolic syndrome (Lefebvre et al., 2006). Part of such anti-inflammatory effect is performed by releasing from PPAR, upon binding

of its agonist, a gene also involved in cancer, BCL6. Two other genes, P53 and PTEN, act in synergy as powerful tumor suppressors (Goberdhan, and Wilson, 2003). To no surprise, then, genetic screening of polymorphisms and expression of such type of master genes and their proximal partners, have revealed traffic jams of informational networks and the risk to type 2 diabetes (Hirschhorn, 2005), obesity, and cardiovascular disease (Barish et al., 2006), and cancer (Lossos et al., 2004).

North-South Collaboration Digital Molecular Medicine in Developing Countries

To test this hypothesis and accomplish its implicit goal it would be necessary to establish two types of connected networks. The first, local, at the South, to link indigenous physicians with scientists of several disciplines; and the second, at the North, made of Rafael Rangel-Aldao hubs from the global innovation systems combining different branches of advanced technologies.

CliniNet would act as a dynamic attractor and connector of the primary and secondary care health sector to biological scientists clustered in BioNet. The latter, would be distributed as nodes of several laboratories from universities and research institutes selected for their capabilities and proven international connections in molecular biology, genomics and proteomics. These laboratories would receive clinical samples (cells) from healthy subjects and patients attended by CliniNet, and perform quantitative studies of the social life of hubs (the usual suspects) that control networks of biological information related to risk and disease of the major causes of morbidity listed above, as explained in hypothesis 1. The analyses would consist of genomic studies of SNPs and gene expression as explained before, or direct studies of protein-protein interactions determined by quantitative proteomics (Blaoev et al., 2004). The interpretation and visualization of such type of data would need the participation of the third type of local network depicted in Figure 2, CompuNet. The scientists of the latter would work very closely with BioNet to apply advanced mathematics and statistical mechanics to figure out the non linear dynamics of gene expression and informational networks that characterize biological systems (Blake et al., 2003). Such

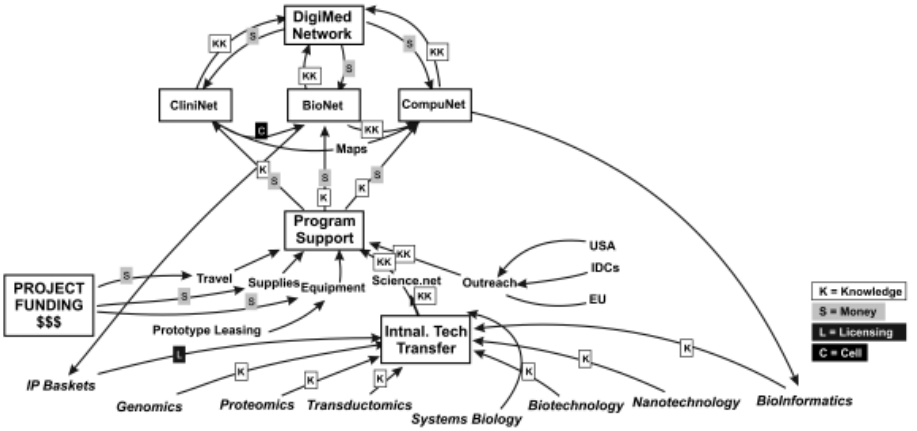

Figure 1. Flows of Knowledge & Funds for Technology Transfer North-South
Networks at the national an international level for technology transfer in digital molecular medicine. Three networks clustered in DigiMed are made of physicians (CliniNet), molecular biologists (BioNet) and computer scientists, physicists, and mathematicians (CompuNet), supported by a national Program to finance international technology transfer from the North, as well as equipment, travel, and supplies for research and development. The flow of knowledge, funds, and cells is indicated with a color code. (Adapted from Rangel-Aldao, 2005)

type of analyses would, in turn, facilitate algorithms to build digital maps of informational pathways to help doctors locate traffic jams and their possible medical solutions to prevent and treat disease early on (Storgaard et al., 2001).

The glue to put and hold together physicians and scientists in countries with little integration of health and science would be the Programme of Support, as indicated in Figure 2.

The programme would use the global supply chain (Friedman, 2005) to circumvent one of the most formidable obstacles to do science in developing countries, the acquisition in time of equipment and supplies, as well as adequate support for travel and conferences. Given enough hard currencies, the whole chain of purchase, transport, and delivery can be outsourced electronically in a synchronous way with the specialized global companies indicated in Figure 2. Administration costs would be minimal since the entire process can be automated electronically with an algorithm that matches the release of funds with fulfillment of specific objectives and deliverables.

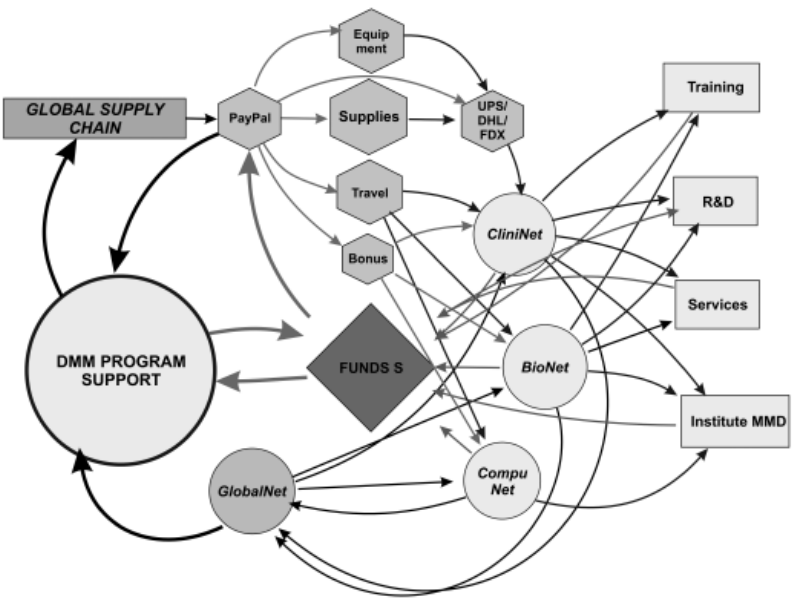

Figure 2. Work Flow & The Global Supply Chain
The global supply chain as a lever of the Program of Support to Digital Molecular Medicine (DMM) in developing countries. Funds in hard currency assigned to cost centers would be synchronized to global companies such as those indicated above (only for illustration purposes) to assure prompt delivery to the local networks. GlobalNet corresponds to the network of laboratories from the North that would transfer technologies to the South.

The Programme of Support would also serve as the bridge to technology transfer from the North by organizing overall funding abroad into a newly made network of laboratories from the frontier of knowledge in genomics, proteomics, bioinformatics, and system biology (GlobalNet). Such laboratories would be offered a wide range of incentives for collaboration such as additional support for ongoing research, travel and exchange, bench fees for training young scientists from the South, cross-licensing of background knowledge, and sharing of intellectual property derived from any foreground knowledge resulting from the cooperation. Another incentive would be a bottom-up approach for bilateral and direct collaboration, that is, partnerships of distinguished scientists from each party, North and South, with little administrative strings given the flexibility of the program of support and the global supply chain.

Impact of Digital Molecular Medicine to Developing Countries

The combined work of physicians and scientists in Digital Molecular Medicine to improve healthcare would address one of the most important obstacles to development and social inclusion, that is, the dissociation of supply and needed demand of knowledge to benefit local communities. Two major areas of development would be directly impacted from this unprecedented association, one, the insertion of researchers into both the mainstream of advanced knowledge worldwide, and also into the response to social demands of their own countries. And, two, as a consequence of the former, the lowering of the burden of disease to developing countries.

North-South technology transfer would create a new type of partnership for economic co-development to share frontier knowledge coming from the 21st century revolution in biology to be translated into better health care for needed regions of less developed countries, as explained below. In addition, the business model of digital molecular medicine also considers its self-sustainability to create wealth, exports, and highly paid jobs, as illustrated in Figure 3:

With respect to the social impact of digital molecular medicine into health care, it is relevant to refer to what WHO has called the burden of disease to establish the consequences of disabilities associated with morbidity, that is, years of life lost through premature death combined with those lived with disability, DALY, (Murray & Lopez, 1996). Because of the demographic revolution it is expected that by 2025 there will be over one billion of people over 60 years old. By 2050, this figure would reach two billion mostly in developing countries (WHO, 2003). At all ages, however, more than 50 per cent of the burden of disease can now be attributed to noncommunicable diseases such as those referred above, cardiovascular diseases, obesity, type 2 diabetes, cancer, and respiratory disease. As an example, the impact of the former disease is illustrated by the following conclusions from the cited study of WHO:

Cardiovascular diseases account for 13 per cent of the disease burden among adults over 15 years of age. Ischemic heart disease and cerebrovascular disease (stroke) are the two leading causes of mortality and disease burden among older adults (over age 60). In developed countries

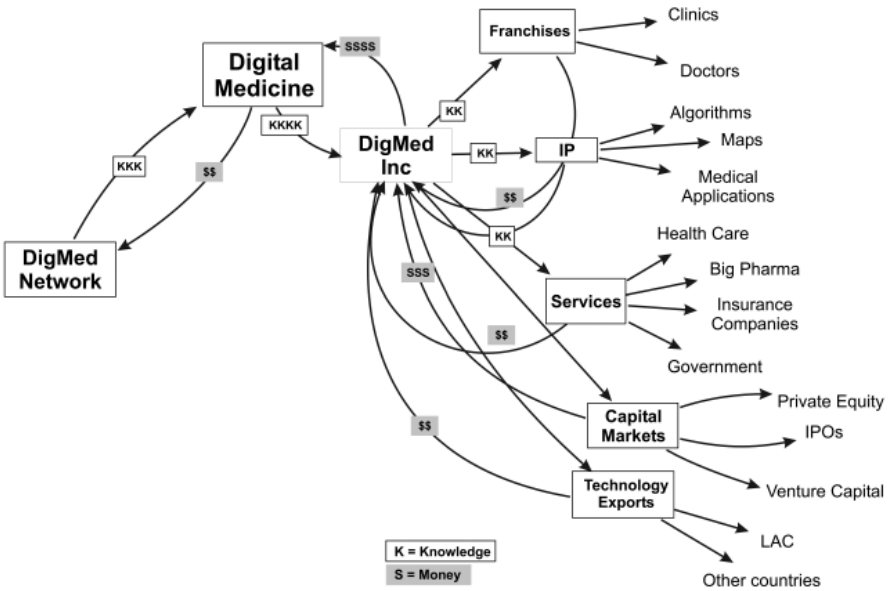

Figure 3. Creation of Wealth and Jobs by Digital Molecular Medicine

Business model of Digital Molecular Medicine. All knowledge created and owned by DigiMed network would be exploited through a civil association of all participants, Digital Medicine, that would own a holding company, DigiMed Inc, to produce revenues from the different sources listed above. Adapted from Rangel-Aldao, 2005.

ischemic heart disease and cerebrovascular disease are together responsible for 36 per cent of deaths, and death rates are higher for men than women. The increase in cardiovascular mortality in eastern European countries has been offset by continuing declines in many other developed countries. In contrast, the mortality and burden resulting from cardiovascular diseases are rapidly increasing in developing regions."

Digital Molecular Medicine, if implemented, could thus significantly lower the magnitude of the burden of disease to developing countries by allowing health systems to launch targeted campaigns of prevention based on population studies of health risks with data from the networks of biological information from each individual. This, as explained above, would be gathered by combining large scale automated genomics and proteomics applied to the molecular hubs that control the path from ER stress to inflammation and from there on to disease.

Conclusion

The road to development and economic growth is paved by scientific knowledge and technology inserted as novel and sustainable solutions to societal needs. For this to occur it is necessary to fulfill at least two major requisites. One, a critical mass of skilled workers well connected to their counterparts from the most advanced nations and; two, effective channels of connectivity between knowledge supply and demand at the national scale. A third factor to add sustainability to the outcome of the first two, is the existence of the necessary incentives to satisfy demand and supply synchronously. The lack of such concurrent conditions may help to explain the mixed results of economic assimilation of advanced biotechnology by many developing countries (Marshall, 2004).

The three conditions could be met by a programme of digital molecular medicine based on international technology transfer North-South, and focused on the major causes of morbidity and burden of disease of developing countries. There is ample evidence to support the three hypotheses set forth to develop such a programme. Emerging knowledge from systems biology combined with state of the art biotechnology is giving a strong back-up to the notion that it is indeed possible to anticipate the onset of disease by epidemiological studies centered on the molecular hubs that control the flow of information of biological networks at the scale of the entire organism or physiome (Buchman, 2002, Rangel-Aldao, 2003). Thus such type of approach could be readily translated to the practice of clinical medicine in developing countries.

For this translation to occur it would be necessary to establish the necessary channels of communication to open a new type of North-South partnership that would lead to not only the transfer of technologies to the South, but to reciprocal exchanges that extend the frontier of knowledge with the results obtained at a massive scale on the health systems of developing countries. The day-to-day difficulties of conducting advanced research at countries of the periphery of science, like most of the developing world, could be tackled by utilizing the global supply chain. That, in turn, would produce a steady flow of knowledge, medical practice, and health benefits to all parties involved, scientists, physicians, and those individuals from entire populations subjected to this new type

of health care combining traditional clinical practice with state of the art technology. From this technology transfer and the co-development of a new system of health care, developing countries could reap enormous advantages that encompass the insertion of science into societal needs, the creation of wealth and new jobs for skilled workers, and well as the lowering of the burden of disease of a growing population.

References

1. Barabasi, A.L. and Ottval Z.N. 2004 'Network Biology: Understanding the Cell´s Functional Organization. Nature Review Genetics 5; 101-113.
2. Barish et al., 2006 Barish, G.D, Narrar, V.A., and Evans, R.M. 2006. 'PPARδ: A Dagger in the Heart of the Metabolic Syndrome' J. Clin. Invest. 116; 590-597.
3. Blake et al., 2001 W.J. et al., 2003. 'Noise in Eukaryotic Gene Expression' Nature 422; 633.
4. Buchman, T.G. 2002. 'The Community of the Self' Nature 420; 246-251.
5. Burrill, G.S. 2005 'The Biotech Meeting at Laguna Nigel. State of the Biotechnology Industry.'
6. Friedman, T. 2005, The World is Flat: A Brief History of the Twenty-First Century. Farrar, Straus and Giroux. New York.
7. Hirschhorn, J. 2005, 'Genetic Approaches to Study Common Diseases and Complex Traits' Pediatric Research 57, 74R-75R.
8. Jeong, H. et al., 2000., 'The Large-Scale Organization of the Metabolic Networks. Nature 407; 651-654.
9. Koonin, E.V. et al., 2002. 'The Impact of Comparative Genomics on our Understanding of Evolution' Cell 101; 573.
10. Lossos, I., et al., 2004. 'Prediction of Survival in Diffuse Large-B-Cell Lymphoma Based on the Expression of Six Genes' NEJM 350; 1828-1837.
11. Luscombe, N.M. et al., 2002. 'The Dominance of the Population by a Selected Few: Power Law Behaviour Applies to a Wide Variety of Genomic Properties' http://genomebiology.com/2002/3/8/research/0040.1
12. Marshall, A., 2004. 'Open Secrets' Nature Biotechnology 22, Supplement.
13. Melton, L., 2003. 'On the Trail of SNPs', Nature 422; 917-923
14. Milo, L., et al., 2002. 'Network Motifs: Simple Building Blocks of Complex Networks' Science 298; 824-827.
15. Murray, C.J.L., Lopez, A.D. eds. 1996 'The Global Burden of Disease: A Comparative Assessment of Mortality and Disability from Diseases, Injuries and Risk Factors in 1990 and Projected to 2020'. Cambridge, MA, Harvard School of Public Health on behalf of the World Health Organization and the World Bank.

16. Ramsawamy, S. 2004, 'Translating Cancer Genomics into Clinical Oncology' NEJM 350; 1814-1816.
17. Rangel-Aldao, R. 2003, 'Developing Countries and Systems Biology' Nature Biotechnology 21; 3-4.
18. Rangel-Aldao, R. 2004, 'Realities for Latin American and Caribbean Biotech' Nature Biotechnolog, 22; 1, 20.
19. Rangel-Aldao, R. 2005, 'Innovation, Complexity, Networks and Health. Innovation Strategy Today', www.biodevelopments.org/innovation/index.htm
20. Service, R.F. 2006 'The Race for the 1K Genome' Science 311; 1544-1546.
21. Storgaard et al., 2001 'Insulin Signal Transduction in Skeletal Muscle from Glucosa Intolerant Relatives with Type 2 Diabetes' Diabetes 50; 2770-2778.
22. WHO 2003 'Global Health Challenges Today'. Geneva, Switzerland.
23. Zhang et al., 2006. 'A Putative Exonic Splicing Polymorphism in the BCL6 Gene and the Risk of Non-Hodgkin Lymphoma' JNCI 97; 1616-161.

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Cancer in the Developing World

Joe Harford

Globally, cancer kills approximately 20,000 people a day, a number projected to increase dramatically in coming decades. In developing countries, the factors driving this projected rise in cancer incidence and mortality include ageing populations, more widespread tobacco use, an increase in obesity and changes in reproductive patterns. The Middle East is, among all the regions of the world, the one where cancer incidence and mortality are predicted to spread most rapidly. Over the past decade the US National Cancer Institute has increased its collaborative activity in the Middle East via bilateral and multilateral partnerships. A look at some of them shows how effective joint efforts can be against a common enemy — in this case, cancer.

Introduction

American baseball legend and amateur philosopher Yogi Berra once said: "It's tough to make predictions, especially about the future." Notwithstanding the difficulties, in healthcare planning it is vital to forecast the burden of diseases societies will have to deal with in coming years. In the case of cancer, the predictions are dire. Worldwide, there are currently over seven million new cancer cases each year and over 11 million deaths from cancer (WHO/UICC, 2005). Cancer today kills more people than

AIDS, tuberculosis and malaria combined and accounts for nearly a quarter of all deaths in the US. While the percentage of total deaths attributable to cancer in poorer countries is generally lower, the developing world's comparatively large population accounts for the fact that today there are more cancer cases and deaths from cancer in the developing than in the developed world. By 2020, it is anticipated that the worldwide death toll to cancer will exceed 16 million, with over 70 per cent of the global cancer burden resting on low- and middle-income countries.

Beyond the sheer size of the developing world's population, a number of other factors contribute to the increasing burden of cancer in these countries. Perhaps most notable the shifting demographics of the planet's population. It has been recognized from the early days of cancer epidemiology that quantitatively, the most important variable influencing cancer risk is age (Armitage and Doll, 1954).

In 2002, it was estimated that 45 per cent of cancers in the world occur in persons above the age of 65 (Ferlay et al., 2004). Worldwide, the median age in the global population is expected to increase from 26 to 36 years by 2050, and the fastest-growing age group will be the over-eighties — rising by nearly four per cent per year, according to the UN report *World Population Ageing 1950-2000*. Whereas the entire population of the world is anticipated to increase by about 50 per cent from 2000 to 2050, the number of people over 65 is projected to rise by about 250 per cent (Bray and Møller, 2006). So one result among many in developing countries with populations that are older on average will be an increasing burden of cancer.

Age is only the tip of the iceberg. Changes in the lifestyles of people living in low-and middle-income countries are likely to contribute to a higher incidence of cancer. Much has been written about these changes (Stewart and Kleihuis, 2003), so only three issues will be mentioned here.

The first is the rise in the use of tobacco products in developing countries, particularly among women who have traditionally smoked less than their male relatives. A recent volume of the International Agency for Research on Cancer (IARC) Monographs Series expanded the list of cancers known to be caused by tobacco from eight in 1986 (IARC, 1986) to 16 in 2004 (IARC, 2004). Of the top eight killer cancers worldwide, six are now known to be tobacco-related, and these six alone account for over three million deaths a year. Currently, lung cancer is the leading

cancer killer of men in the world and in most countries. In the US, where the number of women who smoke has dramatically risen over the last two decades, lung cancer has surpassed breast cancer as the leading fatal cancer in women (Ries et al., 2006).

In the US, excess weight and obesity are second only to tobacco as a cause of preventable death, including cancer. It has been found that keeping weight down, along with physical activity and a diet that includes abundant fruits and vegetables, reduces the risk of breast, colon, oral cavity, lung, cervix, and other cancers (Stewart and Kleihuis, 2003). The US Centers for Disease Control and Prevention estimates that over 60 per cent of Americans over 20 are either overweight or obese. In high-income countries, people are both eating more and exercising less. But a general increase in body weight is not confined to developed countries: the developing world is in transition in this area as well. Whereas hunger remains a problem in many areas of the world, the number of overweight and obese people in low-and middle-income countries is on the rise.

Reproductive patterns are also changing in many regions, as women delay having children, and also have fewer of them than their mothers and grandmothers. These shifts are contributing to a relative increase in breast cancer rates. For instance, there are higher rates of breast cancer in cities compared to rural regions of many low-and middle-income countries (Parkin et al., 1997).

The US National Cancer Institute: International Perspectives

The National Cancer Institute (NCI) is the largest agency within the National Institutes of Health — itself a part of the US Department of Health and Human Services. The NCI's mandate is in large measure stated within the National Cancer Act, which was signed into law in 1971. This and subsequent follow-up legislation recognizes two basic truths: that cancer respects no geopolitical boundaries, and that cancer research discoveries made anywhere can help people everywhere.

Accordingly, the NCI is directed by law to support research in the cancer field outside the United States by highly qualified foreign nationals; collaborative research involving American and foreign participants; and the training of American scientists abroad and foreign scientists in the United States.

With a budget of nearly $5 billion in 2006, the NCI is able to support almost 5000 principal investigators at its Maryland headquarters and at nearly 650 universities, hospitals and other sites in the US and around the world. More than 10,000 medical doctors and 200,000 patients participate in NCI-sponsored clinical trials for treatment, screening and prevention, and nearly 2000 students and postdoctoral fellows are pursuing specialized research training with NCI support.

One of the most visible manifestations of NCI's commitment to training cancer researchers outside of the US can be found in the cadre of international visitors, most of whom conduct basic research in NCI laboratories during their stay at its headquarters. Each year, over 1000 of them contribute to projects at the institute's Center for Cancer Research and Division of Cancer Epidemiology and Genetics while preparing themselves for their own careers in cancer research. Typically, these researchers represent more than 70 countries, including in the Middle East — some of which, such as Iran and Syria, have strained political relations with the US. The contribution of the NCI's international training activities to the worldwide effort to eliminate suffering and death from cancer can be seen in the fact that many of the current leaders in cancer research working around the globe spent time at NCI earlier in their careers. The NCI's many activities round the world (see http://www.cancer.gov) include several that aim to enhance capacity in cancer research in some Middle Eastern countries.

The Middle East Cancer Consortium

The Middle East (WHO/UICC, 2005) is predicted to be one of the regions hardest hit by a dramatic rise in cancer cases and deaths in the coming decades. As a way of combating the problem, the Middle East Cancer Consortium (MECC) was signed into being in Geneva in 1996 by the health ministers of Cyprus, Egypt, Israel, Jordan and the Palestinian Authority. In 2004, Turkey became the consortium's sixth member, making the number of people represented by MECC membership over 160 million. The NCI was instrumental in the establishment of MECC, and continues to support it.

One of MECC's main activities has been the establishment of and support for population-based cancer registries in the region, covering the Republic of Cyprus, Egypt's Gharbia province, Israel, Jordan, Gaza, the West Bank and Izmir province in Turkey. The adoption of common standards in these registries has greatly facilitated data comparisons among them. MECC's *Manual of Standards for Cancer Registry* has been produced in English, Greek and Turkish with plans for an Arabic version well underway. Experts from the US, including a number from the NCI's Surveillance, Epidemiology, and End-Results (SEER) program, have assisted the MECC registries with training, technical support and quality control.

The first peer-reviewed publication arising from MECC activity appeared in 2003. This was the first-ever comparison of cancer incidence rates from Israel and one of its Arab neighbours — Jordan, as it happened (Freedman et al., 2003). Researchers from both countries and the US, including three from the NCI, collaborated on the authorship. Most recent is a monograph comparing data from Cyprus, Egypt, Israel and Jordan with the part of the US population covered by SEER (Freedman et al., 2006).

A few of the major findings presented in this newest monograph are that:

1. Jordanians have the lowest overall incidence of cancer, while Americans and Israeli Jews have a substantially higher incidence and Cypriots, Israeli Arabs and Egyptians had an incidence falling between the two.
2. Liver cancer rates in Egyptians were five-to-seven times as high as those of other MECC populations and more than three times that of Americans — an incidence possibly related to the higher prevalence of hepatitis B and C in Egypt.
3. Egyptians and Israeli-Jews had rates of non-Hodgkin lymphoma higher than that of Americans, and considerably higher than that of other MECC populations.

This is only a sampling of the useful data covered by the monograph, which is available on the MECC website at http://mecc.cancer.gov under 'Cancer Registry Project'. It is hoped that this monograph will stimulate research in the region that will eventually contribute to reducing the burden of cancer in it.

The MECC's activities cover issues ranging from prevention to end-of-life care. Palliative care, for instance, has been identified by the World Health Organization as the highest of priorities *vis-à-vis* cancer for countries with the most severely limited resources. Throughout the developing world, including the Middle East, cancer patients often come to their doctors when the disease is more advanced and so less curable. So building capacity in palliative care and symptom management is all the more pressing in these countries.

The MECC has established a Palliative Care Steering Committee to plan activities in this important area of cancer research and care delivery. And the consortium has sponsored workshops in palliative care, with experts from the US, Europe and the Middle East serving as faculty, and participants representing all of the MECC member nations as well as several other countries from the region. More, because palliative care is relevant to a number of diseases in addition to cancer, the workshops included experts in other diseases. The expansion of MECC's influence in the region beyond cancer was also the theme of an MECC workshop on disease prevention and health promotion. Faculty included international experts in heart disease and diabetes as well as cancer, and the workshop covered smoking and tobacco control activities as well as diet and physical activity.

The past few years have been a difficult period in the Middle East as a whole, and only a handful of activities demanding Arab-Israeli research cooperation have been maintained. Nevertheless, MECC has persevered. Since its inception, it has served as a shining example of how geopolitical differences can be put aside to strive together toward a vital common goal. Aside from its work with MECC signatories, the NCI has been working with the World Health Organization's Cairo office to enhance interactions with other countries in the Middle East. Known as the Eastern Mediterranean Regional Office (EMRO), the office has 22 members, of which three — Egypt, Jordan and the Palestinian Authority — are also MECC members.

One-to-One Partnerships

In recent years the NCI has also initiated bilateral collaborations in the Middle East. Among the most notable has been a project between NCI and the King Hussein Cancer Center (KHCC) in Amman, Jordan, and collaborative activities with the National Cancer Institute in Cairo (NCI-Cairo).

After a memo of understanding was signed with the KHCC in 2002, the NCI detailed one of its staff to serve as the centre's director general, thus providing administrative and scientific leadership. The NCI has also supported needs assessments at the KHCC in nursing, pharmacy, clinical lab/blood banking, radiation oncology, bone marrow transplantation, telemedicine/Informatics and cancer centre administration, and assisted with workshops, symposia and training activities related to a broad range of topics relevant to cancer research and delivery of care to patients.

One of the more significant achievements of the NCI-KHCC was installing a unit of the state-of-the-art video conferencing and imaging system at the centre. Via video conferences and electronic imaging of vital data, cancer specialists can collaborate effectively, remote education and training can take place, and consultations on cancer research protocols and patient care can take place virtually anywhere the system is set up. NCI and KHCC have also collaborated on a number of activities aimed at building capacity in pediatric cancer care delivery in Iraq by providing training courses and fellowships to Iraqi physicians and nurses.

NCI-Cairo — which is affiliated to Cairo University within the Egyptian Department of Education, and is home to the largest cancer treatment facility in Egypt—represents another successful partnership with the US-based NCI. Their joint activities range from supporting the 2004 International Network of Cancer Treatment and Research meeting in Cairo and a collaborative effort between American and Egyptian investigators into tobacco control, to sponsoring the training of Egyptian doctors in lymphoma treatment and of oncology nurses. A project focusing on earlier detection of breast cancer in rural Egyptian villages is to be launched in the very near future.

Conclusion

Cancer is an enemy that recognizes no geopolitical boundaries: every person on the planet is at risk from it. Many think of cancer as a disease of developed nations, but this is a myth: we now know that most of global cancer cases and cancer deaths are already happening in low-and middle-income countries. Looking to the future, it is clear that the burden of cancer on countries both rich and poor will increase.

To cope with this increasing burden of the diseases known collectively as cancer, it will be necessary to enhance capacity for cancer prevention, diagnosis and treatment around the world. It is also clear that more research is needed, and that cancer research should be seen as a shared international responsibility. The US-based NCI, as the largest cancer research body in the world, recognizes its own responsibility to assist in building capacity for cancer research, cancer prevention and cancer care throughout the world. A significant proportion of NCI activities aim at addressing this responsibility in all regions of the world, and individuals from all regions look to the NCI for training.

References

1. Armitage, P. and Doll, R. 1954. 'The Age Distribution of Cancer and a Multi-Stage Theory of Carcinogenesis' British Journal of Cancer 8; 1-12.
2. Bray, F. and Møller, B. 2006. 'Predicting the Future of Cancer' Nature Reviews Cancer 6; 63-74.
3. Ferlay, J., Bray, F., Pisani, P., and Parkin, D.M. 2004. GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide (IARC, Lyon, France)
4. Freedman, L.S., Barchana, M., Al-Kayed, S. et al. 2003. 'A Comparison of Population-Based Cancer Incidence Rates in Israel and Jordan' European Journal of Cancer Prevention 12; 350-365.
5. Freedman L.S., Edwards B.K., Ries, L.A.G., Young J.L. (eds). 2006. 'Cancer Incidence in Four Member Countries (Cyprus, Egypt, Israel, and Jordan) of the Middle East Cancer Consortium (MECC) compared with US SEER'. NIH Publication No. 06-5873. National Cancer Institute, US.
6. IARC. 1986. 'IARC Monographs on the Evaluation of Carcinogenic Risks to Humans', Vol. 38. IARC Press, Lyon, France.
7. IARC. 2004. 'IARC Monographs on the Evaluation of Carcinogenic Risks to Humans', Vol. 83. IARC Press, Lyon, France.

8. Parkin, D.M., Whelan, S.L., Ferlay, J., Raymond, L., and Young, J. (eds). 1997. 'Cancer Incidence in Five Continents', Vol. 7. IARC Press, Lyon, France
9. Ries, L.A.G., Harkins D, Krapcho M. et al., (eds). 2006. SEER Cancer Statistics Review, 1975-2003. National Cancer Institute, US. Available at: http://seer.cancer.gov/csr/1975_2003/, based on November 2005 SEER data submission posted to the SEER web site.
10. Stewart, B.W. and Kleihuis, P. (eds). 2003. World Cancer Report. IARC Press, Lyon. France.
11. WHO/UICC. 2005. Global Action Against Cancer (updated version). WHO (ISBN 92 4 159314 8) and UICC (ISBN 2-9700492-1-X), Geneva, Switzerland.

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New Biotechnologies in Developing Countries: Successes and Constraints

Stephen Jarrett

Introduction

Vaccines are one of the most successful and cost-effective technologies ever introduced in public health. More than three-quarters of all infants in the world are fully immunized against polio, diphtheria, tetanus, whooping cough and measles. It is estimated that these basic vaccines avert more than two million deaths annually and many more cases of illness and disability from vaccine-preventable diseases (WHO, 2005). Smallpox has been eradicated and the global incidence of polio has been lowered by 99 per cent. Measles deaths in Africa have more than halved since 1999 (WHO, 2006). Hepatitis B vaccine has been successfully introduced into over 80 per cent of developing countries and economies in transition, resulting in the prevention of 600,000 hepatitis-B related deaths. All this has basically happened in the last 25 years, as global immunization coverage before 1980 stood at below 20 per cent.

Even in adverse situations, including emergencies and conflict situations, immunization services have been able to reach children with effective vaccines. A specific focus on immunization in the last two decades with international financial support has enabled many countries to maintain a reasonably well-functioning cold chain and systems for monitoring

and surveillance of coverage rates, trends in vaccination and the impact on diseases. Other health interventions for children have begun to take advantage of immunization services, including vitamin A supplementation, de-worming and malaria prevention through the widespread distribution of insecticide-impregnated bed nets. Initial results are proving that if a free or low-cost insecticide-impregnated bed net is provided to mothers once a child is fully immunized, not only are immunization rates higher but malaria incidence is lower.

Immunization Challenge

Two major challenges remain. It is estimated that vaccines still are not reaching 27 million newborns and 40 million pregnant women each year, who are mainly without access to health systems that are under-resourced, both in terms of people and funding. These children and women are those who are suffering most from poverty and more likely to fall victim to communicable diseases. Reaching them is priority in order to reduce child and maternal mortality and to contribute to achieving the Millennium Development Goals.

Secondly, many new vaccines already on the market, or close to market, are under-used or not used at all in developing countries. It is estimated that 2.5 million children under five years die every year from diseases that today can be prevented by using older or newly available vaccines. For this reason, the development and deployment of new vaccines to prevent infectious diseases in developing countries have become high priorities in the global health agenda (Clemens, 2006).

Hepatitis B has been the only major success in the recent introduction to developing countries of an under-used vaccine, with the Global Alliance on Vaccines and Immunization (GAVI) instrumental in supporting the vaccine for low income countries, and with the price dropping to around $0.25 per dose due to the increase in demand. Haemophilus influenza B (Hib) related diseases kill around 400,000 under-five children every year. The Hib vaccine is one of the under-used vaccines that is not progressing as rapidly in its introduction especially into low income countries, even though the vaccine has been associated with a 66 per cent reduction of Hib disease in the Gambia (Mulholland et al., 1997), 31 per cent of pneumonia

cases in infants in Brazil (de Andrade et al., 2004) and 90 per cent or more in the incidence of invasive Hib disease in industrialized countries. At around $3 per dose, countries are cautious about its introduction even with external financial support, because ultimately national budgets will need to take up the funding once international support terminates. In addition, the effectiveness of the Hib vaccine has not been adequately demonstrated in low-income countries, especially those outside Africa and the Americas. Low demand keeps the price high and delays accelerated introduction.

Difficulty in introducing an existing vaccine, such as Hib, augers poorly for a series of promising new vaccines that are due on the international market within the next five years, including rotavirus, human papilloma virus (HPV) and improved pneumococcus and meningococuss vaccines. These are all vital biotechnological tools for the further reduction of morbidity and mortality in children and women, including HPV vaccine as the first vaccine against cancer (Fischmann, 2006). Rotavirus, pneumococcal and meningococcal diseases alone kill 1.1 million under five children every year (WHO, UNICEF, 2005). Decisions on their introduction, nevertheless, have to be based on country disease burden, health priorities and on what is affordable and ultimately sustainable within national budgets.

The vaccine market is expanding rapidly at the global level with annual growth for the industry rising to around 15 per cent per year (Carey, 2002). There is a great risk, however, of further increased inequality between rich and poor countries in the number and type of vaccines they have available to them. Inequalities of income across the globe are actually exceeded by the inequalities of scientific output and technological innovation (Sachs, 1999). With competing health demands, not least of which is the fight against HIV/AIDS, many developing countries may not give sufficient priority to the introduction of new vaccines as a cost-effective health intervention. Placing the right value on vaccines in preventing disease, leading to accurate long-term demand forecasting, constitutes an essential element in their successful introduction to developing countries (Lieu et al.). Paradoxically, the success of vaccination that decreases the threat of disease can act against itself by making side effects more pronounced and questioning its value, exacerbated by vaccines being administered to healthy not sick people, and benefits being only seen in the long term (Greco, 2001). This is seen with polio vaccine where substantial efforts in political commitment, financing, supply and public information are still required to achieve eradication of the disease (Lanet, 2004).

Funding Challenge

Significant international funding is becoming available for vaccines for developing countries, from the Bill and Melinda Gates Foundation and from donor governments, including the launch of the International Finance Facility for Immunization by the UK, France and a number of other countries (Batson, 2005). Long-term international support recognizes the increasing global interdependence of the threat from communicable diseases and can help drive the development and production of vaccines for the developing world. Such support can help subsidize the initial costs of technologies which are likely to be higher at the beginning until demand is high and prices are reduced.

Front-loading of financing is an increasingly accepted means of global support, as can be seen in the International Finance Facility for Immunization, and in the increasing research on Advance Market Commitments which channel funds to cover the initial development and production capacity costs of a new technology. Sure future funding is a critical element of vaccine security, defined as the assured and sustained supply of affordable quality vaccines (UNICEF, 2001). Support for vaccine development and production is insufficient, however, as financial support must also provide the means to increase the decision-making capacity of countries in assessing new technologies and ensuring that systems exist to effectively deliver and use them to public health benefit.

Conclusion

Predictable country demand combined with reliable long-term funding can provide the vaccine industry with sufficient confidence to invest in the production capacities required to meet the vaccine requirement of developing countries. The challenge is to create a balance between a profitable vaccine industry and affordable vaccines for developing countries. It is expected that inequalities of income between countries is recognized by the vaccine industry through differential pricing between rich and poor countries, or rich and poor markets.

Understanding product value in the face of competing demands in resource-poor settings, ensuring sure future funding especially to cover

high front-loaded costs, and investing in delivery systems are the main lessons in introducing new technologies such as vaccines into developing countries. While international support can be vital in the introductory stages of new technologies, it is the country and its resources that will eventually sustain their use. There is increased consciousness around this challenge to long-term sustainability that is driving countries to be more cautious in taking on more expensive technologies. Resource issues have to be taken into account very early in the development of new technologies when these are geared to providing solutions facing developing countries.

References

1. WHO/UNICEF. 2005. Global Immunization Vision and Strategy 2006-2015. WHO/UNICEF, Geneva, Switzerland.
2. WHO. 2006. 'Progress in Reducing Global Measles Deaths: 1999-2004' Weekly Epidemiological Record, No. 10, WHO, Geneva, Switzerland.
3. Clemens J. and Jodar L., 'Introducing New Vaccines into Developing Countries: Obstacles, Opportunities and Complexities' Nature Medicine Supplement 11; 4.
4. Mulholland K., et al., 1997, 'Randomized Trial of Haemophilus Influenzae Type-B Tetanus Protein Conjugate for Prevention of Pneumonia and Meningitis in Gambian Infants' The Lancet 349, April 26, 1997.
5. de Andrade, A. L. S. S. et al., 2004, 'Effectiveness of Haemopilus Influenzae B Conjugate Vaccine on Childhood Pneumonia: A Case Control Study in Brazil' International Journal of Epidemiology 33: 173-181.
6. Global Reduction of Hib Disease: What Are the Next Steps? Proceedings of Meeting, Scottsdale Arizona, September 22-25, 2002.
7. Fischmann J, 2006, 'Sticking it to Cancer' *US* News and World Report, 3 April 2006.
8. WHO, UNICEF, 2005, Global Immunization Vision and Strategy 2006-2015.
9. Carey J., and Capell K., 2002 'Vaccines are Getting a Booster Shot', Business Week, 9 December 2002.
10. Sachs J., 1999, 'Helping the World's Poorest', The Economist, 14 August 1999.
11. Lieu T., et al., 'Overcoming Economic Barriers to the Optimal Use of Vaccines', Health Affairs 24; 3.
12. Greco M., 2001, 'Key Drivers Behind the Development of a Global Vaccine Market' Vaccine 19; 606-610.
13. 'Poliomyelitis-Eradication Initiative's Wider Lessons', The Lancet 363, 10 January 2004.
14. Batson A., 2005, 'The Problems and Promise of Vaccine Markets in Developing Countries', Health Affairs 24; 3.
15. UNICEF 2001, 'Vaccine Security: Ensuring a Sustained, Uninterrupted Supply of Affordable Vaccines'; UNICEF, E/ICEF/2002/6, 21 December 2001.

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Social Responsibility in Healthcare Provision: The Role of the Supercourse

François Sauer

Introduction

The Supercourse is committed to accelerating the acquisition, distribution, translation and validation of worldwide knowledge in preventive medicine, biotechnologies and sciences, to generate behavioural changes that improve individual and community health.

JIT is an abbreviation for 'Just in Time'. In education, just-in-time instruction is available at the time a learner needs it in order to perform a task, rather than only at the time a provider/teacher wants to make it available. JIT describes an action that is taken only when it becomes necessary, such as Just-In-Time compilation or Just-In-Time object activation. By convention, the term 'JIT' alone is used to refer to a JIT compiler (AUDITMYPC, 2006). Productivity: The relationship between production of an output and one, some, or all of the resource inputs used in accomplishing the assigned task. It is measured as a ratio of output per unit of input over time. It is a measure of efficiency and is usually considered as output per person-hour (OJP, 2006).

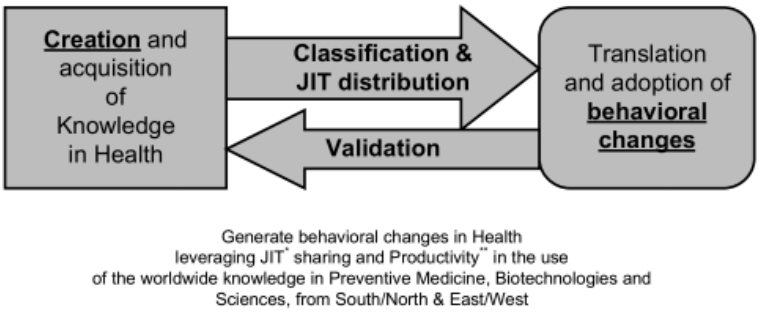


Figure 1. The Supercourse: From Discovery to Delivery Back to Discovery

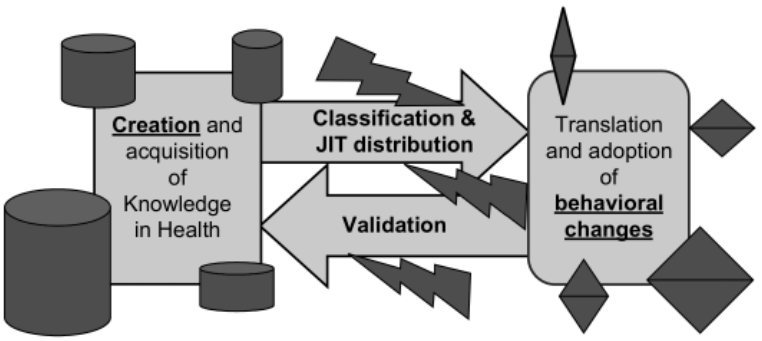


Figure 2. The Current State: Health is a Challenge of our Developing World not of Developed or Developing Countries in Isolation (Silo environment, Fragmentation and Friction in a complex & interconnected world)

Current State Versus the Desired State for Global Health Prevention

The Current State

Today disconnects exist between the knowledge for health available worldwide and the worldwide observed behaviours for health. According to a recent report from the World Health Organization (WHO, 2005), eating healthily, maintaining normal weight, not smoking, and being physically active throughout life can prevent several non-communicable

diseases (NCDs). These include up to 80 per cent of cases of coronary heart disease; 90 per cent of type 2 diabetes and one-third of cancers.

The UN Millennium Action Plan tells us that new technologies hold great potential for improving health care, primarily by increasing the quality, relevance and flow of information to health personnel. However, in many countries, we are far from having exploited this promise. This is due not only to financial, technological and infrastructure challenges as the term 'digital divide' suggests, but also because the real needs of the users — which vary greatly due to educational, social and cultural differences — are often overlooked. (UN, 2000)

The Desired State

As we address through better communication, cooperation and coordination the current friction and fragmentation we are faced with, the concurrent challenge is to create a powerful engine to provide additional traction or trust for the growth of global health prevention, addressing the real needs of the users. The Supercourse is presented as one element to build this powerful engine to grow global health prevention.

Any powerful engine generates frictions. Therefore our Social Responsibility for Health is the required context to balance the friction and the power of the engine. We can look at our Social Responsibility for Health from two perspectives: 1) as a 'donation' that will address specific current 'friction and fragmentation' challenges and 2) as a systemic investment to leverage over time the productivity and quality of the life of the community.

Social responsibility can be viewed as part of our social contract. It is the responsibility of each entity whether it is state, government, corporation, organization or individual to contribute to society at large, or on a smaller scale. In a way it can be traced back to ideas such as the golden rule of treating others as you would want to be treated. "Corporate Social responsibility goes beyond charity and requires that a responsible company will take into full account the impact on all stakeholders and on the environment when making decisions." (Wikipedia, 2006)

The Space and Time Challenge

The global health initiative is designed to support health prevention from a Just In Time (JIT)/long term and global/local perspective because today we are faced with the facts that:

- The creation of new knowledge is experiencing an exponential growth.
- Many threats to health need to be identified from a JIT and a long term mode, for example Avian flu.
- Through genetics we can now assess the risk level of a person for some specific pathogen agents. For example Shigella Salmonella (food born) may trigger the Reiters Syndrome in people with HLA B27+.
- People in need of healthcare need very specific JIT options, which integrate as much as possible the world's experience. One example for this potential cooperation is for experts in West Nile Virus from Egypt, to help manage and prevent new local cases in Kansas and Missouri. As of 2006, 4000 cases of West Nile Virus were reported in the United States.

Because behaviours are manifested in a complex system it is critical to then over time assess their effectiveness in order to learn, evolve and adapt. We want to see beyond the horizon of the 'here and now' and validate our capability to anticipate long term and global consequences.

Today a car, with a Global Positioning Systems (GPS) and an automatic intercommunication capability with surrounding cars, can be JIT aware of its traffic status knowing the obstacles in the terrain and its own relative position versus other cars. Then using a dynamic simulation model the car can assess the probability of an impending collision and take proactive measures. This capability was demonstrated in "a Motorola project, where transponders were housed in small grey boxes affixed to light poles along several kilometers of local streets in Farmington Hills." (Dizikes, 2006)

Today, in health prevention this GPS/JIT proactive behaviour style can be leveraged by hand held devices like cell phones, PDAs and PCs interconnected with a portal. For example, an article in *The Economist* print edition from 24 March 2006: 'The Medical Uses of Mobile Phones Show They can be Good for your Health' documents that text messages in health prevention have been used in India to inform people about the

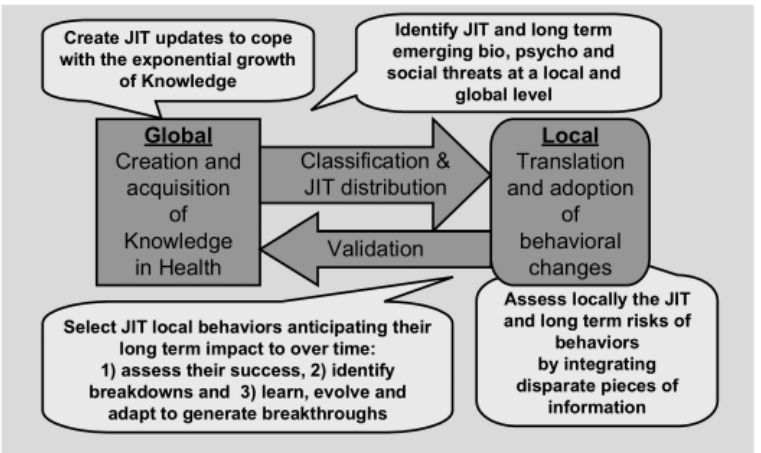


Figure 3. The Space & Time Challenge

World Health Organization's strategy to control tuberculosis, in Kenya, Nigeria and Mali to provide information about HIV and malaria, and in Iraq to support a campaign to vaccinate nearly five million children against polio.

As we face an explosion of knowledge, the challenge is how to address the complexity and operational constraints that limit the effective translation of knowledge into behaviours. This challenge is compounded by four additional environmental facts according to the World Health Organization (WHO, 2006):

- We are facing an estimated shortage of almost 4.3 million doctors, midwives, nurses and support workers worldwide.
- We need to shift successfully to community-based and patient-centred paradigms of care for the treatment of chronic diseases moving away from the traditional escalation of care with MD and hospital care.
- We need JIT knowledge to tackle the problems posed by disasters and outbreaks.
- We also need to preserve health services in conflict and post-conflict states.

So the resulting challenge is: how to manage knowledge with a shorter and shorter shelf life within a very dynamic delivery structure and a shortage of health professionals?

The Lineal and Systems Thinking Challenge

The Supercourse is committed to addressing how to translate nuggets of knowledge or generic lineal cause-effects statements, scientifically validated and replicated in laboratory conditions, into effective behaviours for health manifested within a complex ecosystem that is unique for each individual, within his/her community. We want to develop our capabilities to see the systems we are part of. Our challenge is to understand that we are part of 'one developing world' leveraging through this awareness our solidarity and social responsibility for health.

Now we are evolving from organism genomics to ecological metagenomics. This systems thinking evolution is having a dramatic impact on life sciences research because in a complex system the initial conditions impact the behavior of the system and they may be very difficult to replicate.

When we are translating knowledge into behaviour we now speak about environmental genomics data that can involve a wide range of data types, including: ecological data, population fingerprint results, niche definitions, and sample provenance data as well as molecular data such as sequences, gene expression, metabolome (pathway), and proteome data.

Our challenge is to create an environment that empowers the individual to validate and improve the learning cycle, where knowledge is translated into behaviours that are over time assessed for their effectiveness to then generate new knowledge.

The people exposed to new knowledge first have to agree that this new knowledge is trustworthy and useful for that knowledge to be translated and assimilated into productive behavioural changes. The success of the translation depends on factors including: the vocabulary used, the mindset and culture of the recipient of the message, and his/her level of independent thinking and education.

An example of this challenge to locally translate and assimilate relevant knowledge can be illustrated with the article in CBS News 'Polio Outbreak After Vaccine Ban' KANO, Nigeria, July 2, 2004: (CBS/AP) "A suspected large-scale polio outbreak was reported Friday among children in a heavily Muslim northern Nigeria state that had boycotted immunization campaigns, and local authorities appealed for urgent action to stop the spread. The suspected outbreak was in Kano state, one of several in northern Nigeria

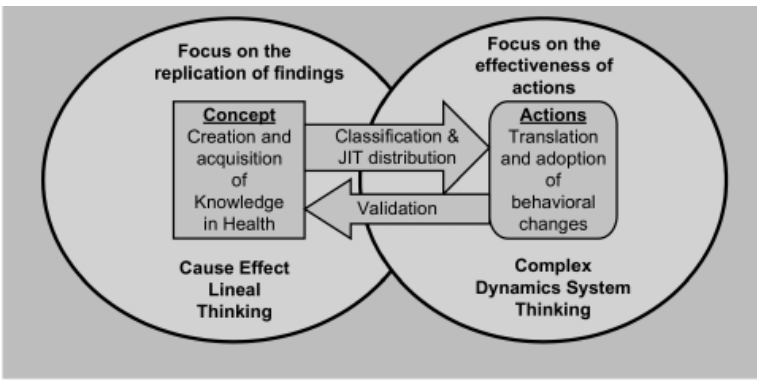


Figure 4. The Lineal and Systems Thinking Challenge

that had shunned polio vaccination drives over suspicions the vaccines were part of a US-led plot to render Muslims sterile. As we know from WHO reports, polio has then spread from there, by the end of 2005, to many previously polio-free countries including Indonesia, Nepal, and Yemen" (CBSNEWS, 2006).

Acknowledging the sharp contrast between the food that is consumed and the knowledge that circulates we can highlight some parallels. To create 'translation ready' knowledge is like delivering a dinner *a la carte* incorporating cultural constraints (taste and trust) and physiological constraints (assimilation skills). The teacher is for the translation and assimilation of knowledge what the cook is for the presentation and assimilation of food. From a community perspective, the investment, to support research, is only relevant if the research's results and the expert knowledge created for health are widely circulated, updated and translated into practice through productive behavioral changes. No behavioural change means a productivity of zero for the knowledge proposed.

The Social Responsibility and Trust Challenge

Social Responsibility for Health is required for the building of a powerful engine with traction for global health prevention. We want to stimulate the cycle to improve health leveraging the creativity of this network of networks between academy, industry, NGOs and governments. One example of this systems/business approach is the Sauri project in Kenya.

This is the first beneficiary of the UN Millennium Village Project that has begun 18 months ago (Chron, 2006).

Another example is in Mexico were the IT firm HP received the CEMEFI (The Mexican Center for Philanthropy's Socially Responsible Company award) for the 5th consecutive year (HP, 2006).

Today we operate in a world that is culturally, technologically and financially interdependent. The sustained development of health requires the participation of all the stakeholders of the community. We know that the health status of a nation is a key component for its productivity and we also know that an increase in productivity is a very powerful lever to re-distribute wealth in a nation therefore decreasing poverty and consequently increasing health. In global health prevention what is relevant is the exercise of social responsibility for intercommunication, cooperation and coordination between academy, industry, NGOs and governments to build an engine for growth that enables, within a network of networks, the sharing of knowledge for health, acknowledging that the stakeholders in health have different languages and priorities. By engaging the best minds in the world, accelerating the speed of the translation of knowledge for health into behaviours and over time assessing the demonstrated effectiveness of these behaviours, we can then become better and better at preventing and curing diseases as we now better anticipate the long term and distant consequences of present actions from a multi-disciplinary and systems perspective.

To illustrate with an historical case the impact of the lack of circulation of knowledge we can mention that the last outbreak of polio in Canada and the United States, in 1978–1979, was the result of travel from the Netherlands, where an outbreak was ongoing, to Canada by members of the Reformed Netherlands Congregation, a religious group that refused vaccinations (CDC, 2006).

In 1978 the Canadian and the US health authorities were not aware that a polio outbreak was ongoing in the Netherlands. As we know microbes and viruses don't respect borders. The first challenge therefore is to create a better level of JIT global awareness about the state of infectious diseases.

Now to address the risks associated with the universal circulation of knowledge we can ask the question: how to raise the confidence level that abundance is feasible so each individual knows that building together a

better quality of life from a bio, psycho and social perspective is an option that is available.

The Value Added of the Supercourse

Our challenge is to build a curriculum to *change* versus a traditional curriculum to *last*. To achieve that we propose for the Library of Alexandria and Supercourse to address the multi disciplinary and systems integration of the following attributes to expand the Supercourse:

Reputation:

- Brand equity of integrity.
- Capability to integrate worldwide South/North and East/West cultural diversity.
- Compatibility with local community values.

Human resources:

- Scientists volunteer base trained in the latest technique and new knowledge.
- Ability to mobilize and coordinate volunteer base.
- Experience in developing and delivery certification programmes.

By systems we mean that the Supercourse penetrates the fabric of our community – The formal definition is: Spread throughout the body; affecting many or all body systems or organs; not localized in one spot or area (MIT, 2006).

Infrastructure:

- Ability to create service, center and leverage existing IT and telecom technologies to leverage the productivity of the learning cycle in health prevention
- Pervasive Internet access for JIT sharing

Capabilities:

- Capability to attract, nurture a global health network & zoom in to coordinate at the community level
- IT systems sophistication to incorporate forecasting systems and other advanced technologies in classification and search engines

- Ability to connect and sustain a partnership for health with academy, industry, NGOs and governments
- Ability to recruit and organize a network of teachers for global health
- Accumulated experience in the circulation, translation and assimilation of knowledge
- Ability to create organization with effective communication, cooperation and coordination of network of networks.

References

1. AUDITMYPC, 2006. http://www.auditmypc.com/acronym/JIT.asp
2. CBS News, 2006. http://www.cbsnews.com/stories/2004/07/19/health/main630608.shtm/
3. CDC/ mmwr. 2006. 'Epidemiologic Notes and Reports Follow-Up on Poliomyelitis—United States, Canada, Netherlands', MMWR July 1979 http://www.cdc.gov/mmwr/preview/mmwrhtml/00050435.htm
4. CDC/ncidod, 2006 http://www.cdc.gov/ncidod/dvbid/westnile surv&control06Maps PrinterFriendly.htm
5. Chron, 2006, http://www.chron.com/disp/story.mpl/world/3780305.html
6. Dizikes, P., 2006, 'Wireless Highway with Sensors in Cars and Transponders on Poles, Networked-Car Safety Research is Hitting the Road', MIT Technology Review. http://www.technologyreview.com/InfoTech/wtr_16448,294,p1.html
7. HP, 2006. http://www.hp.com/hpinfo/globalcitizenship/gcreport/intro/globalcitizen.html
8. MIT, 2006, http://web.mit.edu/environment/ehs/topic/HazCommTerms.html#S
9. OJP, 2006, http://www.ojp.usdoj.gov/BJA/evaluation/glossary/glossary_p.htm
10. UN, 2000, 'The United Nations Millennium Action Plan', http://www.unmillenniumproject.org/
11. WHO, 2005, 'Towards a Global Strategy on Diet, Physical Activity Health, http://www.who.int/entity/mip/2003/other_documents/en/Pekka'sper cent20Pr esentation.pdf
12. WHO, 2006, Working Together for Health' http://www.who.int/whr/2006/en/index.html
13. Wikipedia, 2006, http://en.wikipedia.org/wiki/Social_responsibility

25

Preventing Genetic and Congenital Disorders at Birth

Ysbrand Poortman

Introduction

The toll of genetic and congenital diseases has recently been charted by the March of Dimes Birth Defects Foundation. It has been estimated in a recent report (MoD, 2006) that worldwide, the birth prevalence of all genetic and congenital diseases range from a high of 82 per 1000 live births in low-income regions to a low of 39.7 per 1000 live births in high-income regions.

The alarming results of this study more than justify collaborative national and international initiatives for care and prevention of these diseases and disorders. These initiatives should be based on local and regional needs, assessment of barriers and bottlenecks and based on an appropriate network of high quality, easily accessible genetic services integrated in the primary and secondary healthcare system and on multi-stakeholder partnerships.

Patient groups have united in alliances on the national, regional and global level to focus on disease specific interests, on social issues or on prevention and treatment of these diseases. They play an increasing role in developing strategies that seek to prevent birth defects and to improve the care for individuals, families and communities affected by these disorders.

They also contribute to the research effort, into prevention and treatment and to care delivery.

Definitions

Birth defects are defined as any abnormality affecting body structure or function that is present from birth. They may be clinically obvious at birth or may be diagnosed later in life.

The term 'birth defects' is synonymous with the term 'congenital disorder' as defined and used by WHO and both terms can be used interchangeably. Patient groups do not like the term 'birth defects' but prefer 'genetic and congenital conditions'. The terms 'diseases', 'disorders' and 'conditions', although they have different emotional and semantic aspects, can also be used interchangeably.

Birth Defects and Their Toll

Every year an estimated 7.9 million children -- six per cent of total births worldwide -- are born with a serious birth defect of genetic or partially genetic origin. Hundreds of thousands more are born with serious birth defects of post conception origin, including maternal exposure to environmental agents such as alcohol, rubella, syphilis and iodine deficiency.

Serious birth defects can be lethal. For those who survive, these disorders can cause lifelong mental, physical, auditory or visual disability. Many conditions result in multiple impairments affecting a wide range of body systems. At least 3.3 million children under five years of age die from birth defects each year and an estimated 3.2 million of those who survive may be disabled for life. Early in 2006 the March of Dimes published and promoted a report in which the toll of birth defects was documented. This report is the first to provide worldwide estimates of the prevalence for serious birth defects of genetic and congenital origin.

Most Frequent Birth Defects

The five most frequent serious birth defects account for about 25 per cent of all birth defects of genetic or partially genetic origin. These are congenital heart defects (more than a million per year), neural tube defects (more than 150,000 per year), hemoglobin disorders such as thalassemia and sickle cell disease (more than 150,000 per year), Down's syndrome (over 200,000 per year) and glucose-6-phosphate dehydrogenase deficiency (between 150,000 and 200,000 per year). Each group of these birth defects requires a specific approach regarding how to deliver appropriate services for prevention and for the care of those affected and for support to families at risk.

Birth defects are a global problem but their impact is particularly severe in middle and low income countries. More than 94 per cent of the births of children with serious birth defects and 95 per cent of the deaths of these children occur in middle to low income countries. Over the last 40 years these countries have been active in improving healthcare resulting in a reduction in population mortality. This positive health transition is marked by decreasing occurrence of infectious diseases and malnutrition. This is mirrored by declining infant and under five mortality rates and increased population life expectancy.

Unfortunately, rates of birth defects have not decreased. This is a special tragedy because up to 70 per cent of birth defects could either be prevented or the children affected offered care that would be life saving or significant in reducing aspects of any resulting disability (Christianson & Modell, 2004; Czeizel et al., 1993)

Millennium Development Goals

In 2000 the United Nations announced its Millennium Development Goals for 2015. These were wide ranging but one of the big goals is to reduce under-five child mortality by two-thirds from the 1990 base.

Experience from high income countries presents the possibility of preventing, ameliorating or treating up to 70 per cent of birth defects. Given that this is so, what are the barriers that block action to reduce so significantly the burden of birth defects?

A fundamental problem is the low priority given to this major health issue by health policy makers, public health officials and the medical profession due to a lack of awareness of the incidence and prevalence of birth defects and of the cost implications of lifelong disability.

Moreover there is a widespread misunderstanding that effective care and prevention of birth defects require costly, high-technology services at a tertiary specialist level that developing countries cannot afford. While this may be the case for some conditions a great deal of care and prevention can appropriately and routinely carried out in primary and secondary healthcare settings.

Other barriers are created by poor socio-economic status of families at risk (poverty, illiteracy), low levels of pre conception maternal and child healthcare, absence of integrated networks of genetic services (lack of experienced geneticists and primary health care providers trained in genetics) and many other unmet needs (for example, infectious diseases, malnutrition, sanitation, labour and delivery care) which need to be addressed.

Approaches to Reducing the Toll of Birth Defects

Impressive progress in the life sciences and in biomedical technologies increasingly enable an understanding of the causes of genetic and congenital diseases and provide tools for prevention and treatment. For many diseases there are simple tests for early detection, neonatal screening and for carrier identification that facilitate preventive strategies. For an increasing number of diseases new, often biotech based, drugs have been developed and put on the market.

A prerequisite for an effective approach to reducing birth defects is the availability of competent networks of medical and genetic services for care and prevention. In addition to this public awareness, political will and governmental commitment are a necessity for success. There is no standard set of interventions that can be recommended for universal application due to regional and national differences in needs and priorities, epidemiology, demographic factors, organization of health care systems and available resources.

For each region or country and for each group of birth defects strategies need to be developed. Whilst specifics will vary from country to country, and from disease to disease, such strategies are like to have in common the need for genetic networks, for quality assessment and evaluation, resources, public awareness and communication on the international level.

Recently, ministries of health, major international institutions and professional and lay organizations are creating joint ventures to counteract the implications of birth defects. An example of such collaboration is the coming together of the World Health Organization (non-communicable diseases), US based Centers for Disease Control and Prevention, the Global Programs of the March of Dimes, the World Alliance of Organizations for Prevention and Treatment of Genetic and Congenital Conditions and the International Genetic Alliance of Parent and Patient Organizations (IGA).

The report of the March of Dimes Birth Defects (New York, 2006), acknowledged by a WHO expert meeting (Geneva, May 2006), sets the scene by presenting explicit data of the toll of birth defects per country of the impact of these conditions and gives recommendations for services for care and prevention. The mission of the March of Dimes Birth Defects Foundation is to improve the health of babies by preventing birth defects and infant mortality. March of Dimes Global Programs builds on the Foundation's strengths by developing and implementing innovative programs to promote perinatal health worldwide.

The World Alliance, founded by the March of Dimes in 1994, and working together with the March of Dimes Global Program, committed itself to:

- Establishing strategic partnerships to connect authorities, (primary and secondary) healthcare officials, academia and parent/patient/community groups.
- Supporting the development of coordinated strategy and action plans based on the advances in genetics, genomics and biotechnology focusing on regional needs and priorities and the optimal use of already-available expertise and facilities.
- Encouraging the establishment of network of competent genetic services integrated in primary and secondary healthcare systems.

- Encouraging advocacy initiatives at global, regional and country levels for increased awareness and mobilization of resources and support.
- Appreciating ethical principles.

The World Alliance has a strong partnership with the International Genetic Alliance through structural participation at board level, in projects and activities, in particular towards joint ventures with groups in developing countries.

The International Genetic Alliance (IGA) is an alliance of continental and regional alliances of parent/ patient/family organizations with an involvement in the opportunities and implications of genetics, genomics and biotechnology regarding its potential for prevention and treatment of serious disease. IGA's vision is a 'world in which genetic diseases and acquired birth disorders are understood, prevented and cured and those affected well supported'. IGA promotes medical genetic services, technologies, access to information, in order to alleviate the burden of genetic conditions for individuals, families and communities. IGA was founded in 2000 and brings now over 2000 parent/patient organizations together through a global network of regional and national alliances and patient led umbrella groups.

Parent/patient and family organizations are a new and potentially powerful partner for increasing public awareness, supporting families, contributing to education and the provision of tailored, balanced and reliable information, ensuring effectiveness and equity in medical genetic services. They also lobby for increased investments in research and development of genetic services and other interventions for care and prevention of birth defects.

IGA joins the World Alliance in developing strategies for identifying health system barriers and to address them through communication and strategic partnerships.

Some routine aspects of such a strategy are:

- To raise awareness of the need for prevention and care of congenital and genetic disorders among governments, development partners, and the medical profession.
- To encourage better use of existing resources to address defined needs.

- To enhance the scale of implementation of proven interventions.
- To identify gaps in knowledge, communication and resources.
- To stimulate of research initiatives.
- To empower patient, family and community groups.
- To promote education in biotechnology for non-genetics health professionals.

The World Alliance -- in cooperation with the March of Dimes and national organizations -- has co-organized major conferences in The Hague, Amritsar, Johannesburg and Beijing and is in the process of co-organizing such conferences in Rio de Janeiro and Oman.

The meeting in The Hague was an expert meeting jointly organized with the WHO in 1999, and in which 27 experts from 19 countries participated. The report of the meeting ('Services for the Prevention and Management of Genetic Disorders and Birth Defects in Developing Countries' WHO, 1999) is a comprehensive list of recommendations that are still relevant today.

They are:

- Chart and recognize the burden imposed by genetic disorders.
- Improve epidemiological knowledge about genetic disorders.
- Define goals of genetic services in terms of individual family well-being and public health.
- Improve prenatal and perinatal services.
- Organize genetic services that are comprehensive and integrated 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.

Medical Genetics Services Integrated in Public Health

Medical genetics services in low-and middle-income countries should be based on a continuum stretching from peri-conception care, maternal health, management of labour, to newborn and child health care for infants and children with acute and chronic disorders. Services for the care and prevention of birth defects must also link to and build on programs

in nutrition, immunization, infectious disease control and disability and rehabilitation. In addition, medical genetics services should have a strong base in primary health care and be integrated with secondary and tertiary health care services.

Medical genetics services should emphasize both care *and* prevention. Care includes the recognition and diagnosis of birth defects; treatment involving therapeutic, surgical and neurodevelopmental therapy; and counselling with psychosocial support. Care can be cost-effective as is seen, for example, with the diagnosis and surgical treatment of common malformations such as certain cardiac defects (Christianson, 2006; Christianson and Modell, 2004; WHO, 1999).

Medical genetics services should also focus on the implementation of basic reproductive health approaches, best provided as part of peri-conception care. Such services include family planning and optimizing women's health through, for example, improving diet, optimal treatment for significant illnesses such as bype-1 diabetes mellitus and epilepsy.

Medical Genetics services Targeted to Period-Specific Strategies

A range of interventions is possible, but these must be targeted at the appropriate stage of pregnancy and the neo-natal period if they are to be effective.

Preconception

1. Carrier identification using family pedigrees.
2. Carrier screening for common recessive disorders, the haemoglobin disorders (FBC & indices, electrophoresis, DNA) and cystic fibrosis (DNA).

Antenatal

3. Rhesus status.
4. Down syndrome (advanced maternal age, maternal serum, ultrasound).
5. Neural tube defects (maternal serum & ultrasound).
6. Major malformations (foetal anomaly scanning).

7. Carrier screening for common recessive disorders, the haemoglobin disorders (DNA) and cystic fibrosis (DNA).

Postnatal

8. Neonatal screening.
9. Congenital hypothyroidism.
10. Sickle cell disorders.
11. Neonatal jaundice /G6PD deficiency.
12. Inborn errors of metabolism

Medical Genetics Services Targeted to Disease-Specific Approaches

For the five most frequent serious birth defects mentioned above, specific services are available. Hemoglobin disorders such as thalassemia and sickle cell disease are single-gene defects, which have a high prevalence in certain parts of the world. This is in part due to consanguinity. Carrier testing and genetic counseling could significantly reduce the prevalence. In some countries such as Cyprus and Sardinia the occurrence of these diseases has been reduced to almost zero by the provision of appropriate counseling, services and support. The incidence of some chromosomal disorders such as Down syndrome could be reduced by awareness of the risk associated with advancing maternal age. The incidence of neural tube defects can be significantly reduced by pre conceptional administration of folic acid.

Medical Genetics Services Targeted to Reproductive Approaches

Family planning

Promote family planning, allowing couples to space pregnancies, plan family size, define the ages at which they wish to begin and complete their families and reduce the proportion of unintended pregnancies. This will:

- Reduce the overall rate of birth defect.

- Decrease the birth prevalence of Down syndrome by reducing the number of mothers of advanced maternal age.
- Allow women with affected children the option of not having further children.
- Introduce women to the concepts of reproductive choice.

Maternal health and nutrition

Ensure a healthy, balanced diet before and during a woman's reproductive years through an adequate intake of macronutrients (protein, carbohydrates and fats) and a broad range of micronutrients. This will:

- Prevent iodine deficiency disorder through fortification of salt with iodine.
- Prevent neural tube defects and other malformations through fortification of flour and other staple foods and through folic acid supplementation where required.
- Reduce birth defects due to common teratogens such as alcohol and recreational drugs.

Infections

Control infections in women before and during pregnancy. In particular:

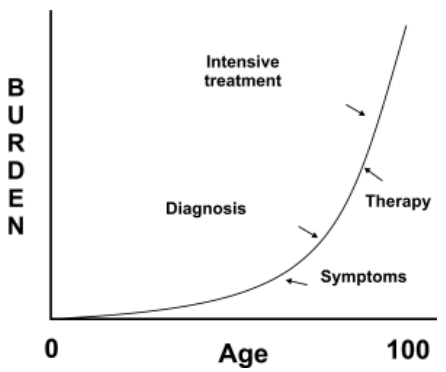
- Prevent and treat syphilis.
- Pevent congenital rubella syndrome through immunization.

Trends in Healthcare

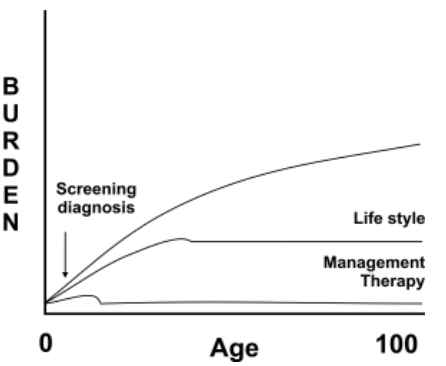
Over the last half century there has been a shifting pattern of possibilities for intervention. Half a century ago little was known about the causes of conditions which appeared before or around the time of birth. As science progressed ignorance gave way to inconsistency, where it was known that certain conditions were congenital, but why was unclear, through diagnosis to the possibility in an increasing number of cases to intervene in ways that will allow early (pre-natal) diagnosis, risk assessment, counseling and for more and more conditions practical interventions for prevention, management or cure (see Box, **Trends in Healthcare**).

Trends in Healthcare		
1.	1950 – 1960	Ignorance
2.	1960 – 1970	Uncertainty
3.	1970 – 1980	Diagnosis
4.	1980 – 1990	Quality of life
5.	1990 – 2000	Management
6.	2000 – 2010	Prevention, testing/ screening
7.	2010 -	Timely & well informed decision making Individualized medicine

Typically health systems around the world invest the bulk of their available resources in responding to extant disease. This has the result of concentrating resources at the end of life, when often little can be done beyond palliation of symptoms and provision of added quality of life for those already sick. Whilst this is an admirable aim, and it must not be overlooked or minimised, it does little to prevent disease from emerging or to reduce the impact of disease on individuals and families at risk.



Graph 1: Healthcare resource allocation and disease burden: current patterns of provision.



Graph 2: Healthcare resource allocation and disease burden given the development of effective programmes for reducing birth defects.

The advances in our understanding of the links between genes and health and disease allow us to plan for a future where early interventions, possibly even in the pre-symptomatic phase of the development of

an illness will allow for the introduction of preventative therapies or other forms of treatments which will either remove the cause of the condition, stop its further development beyond the point of introduction of treatment or even provide a cure or a long term remission. This not only reduces the burden of disease on families, it also allows for the introduction of a public health based programme of service delivery that combines life style measures with management and therapy that reduces demand for resources by changing the trajectory and impact of the disease (Graph 2).

Conclusion

The toll of genetic and congenital diseases is enormous and much underestimated. This is particularly alarming in medium and low-income countries where more than 90 per cent of the world's children are born. Over the last decade molecular biology and medical technologies have greatly advanced and are now offering new tools for early detection and accurate diagnosis. New sciences have emerged such as genomics, proteomics, systems biology, bio informatics all of which contribute to better understanding of the mechanisms causing disease, laying a comprehensive basis for strategies leading to prevention and treatment of genetic and congenital disorders.

New approaches in terms of multi-stakeholder commitments and strategic partnerships and the application of the many recent scientific achievements in terms of early detection and appropriate care linked to comprehensive medical genetic services can reduce considerably the toll of birth defects. In contrast to what is often perceived these services -- if integrated in public healthcare – are cost effective.

Some of the approaches are timely folic acid supplementation, iodized salt, good maternal nutrition, vaccination programs to avoid congenital infections, avoidance of environmental teratogens and giving women more control of their reproductive options.

"No matter our own personal interests, or the concerns of the countries we represent, we are all working for the same goal: a future where all babies are born healthy and where every child born with a birth

defect receives appropriate care, and can grow up to live a productive and healthy life. All countries in the developing world should unite for a future of Healthy Children throughout the world." (Concluding sentence of the Manifesto adopted at the 2nd International Conference On Birth Defects and Disabilities in the Developing World, held in Beijing, China in September 2005).

Acknowledgements

Much data in this chapter are taken from the 'Global Report on Birth Defects' of the March of Dimes Foundation and from a report of an expert meeting of the WHO on the same subject which took place in Geneva, 17-19 May 2006. I am indebted to Arnold Christianson, Alastair Kent and Irmgard Nippert for their help in preparing this paper and who all contributed to the Global Report of the March of Dimes and participated in the WHO expert meeting in Geneva.

References

1. World Health Organization, 1999, 'Services for the Prevention and Management of Genetic Disorders and Birth Defects in Developing Countries', WHO/WAOPD, WHO, Geneva. WHO/World Alliance Conference the Hague.
2. World Health Organization, 2000, 'Primary Health Care Approaches for Prevention and Control of Congenital and Genetic Disorders, WHO, Geneva. WHO Conference, Cairo.
3. Poortman, Y.S. and Eskes, T., 2004, 'The Increasing Role of Nutrition and Genomics in the Prevention and Management of Disease', Aspekt, Soesterberg
4. Poortman, Y.S., 2004, 'Global Partnership of Scientists, Doctors and Patient Organizations' *From Discovery to Delivery*, report of BioVision Alexandria, p. 295-300.
5. March of Dimes, 2006, 'Global Report on Birth Defects: The Hidden Toll of Dying and Disabled Children', March of Dimes Birth Defects Foundation, White Plains, New York.
6. World Health Organization, 2006, 'Services for the Care & Prevention of Birth Defects, WHO, Geneva. WHO/March of Dimes Conference, Geneva.

5

DIABETES IN DEVELOPING COUNTRIES

26

The War on Diabetes: A View From Industry

Boerge Diderichsen

Diabetes is a public health problem of global proportions. In 2003, 194 million people had the disease — a number that will increase to 230 million in 2007 and is expected to reach 333 million by 2025 if nothing is done. Diabetes is associated with vascular complications leading to blindness, kidney failure, amputations and a threefold increase in cardiovascular morbidity and mortality. In 2007, diabetes will cause 3.5 million deaths. Beyond the human cost, the economic burden is severe. Poorer people, including millions in the developing world, will suffer — and because they are less able to get access to proper healthcare, are at risk of becoming a heavy economic and social burden. The impact of diabetes on society, already massive, will be catastrophic in the future if nothing is done to offer better prevention and care.

Introduction

The terrible impact of infectious diseases in developing countries is well known and amply documented. What is less well understood is that migration from rural areas to urban, along with demographic changes and increasingly sedentary lifestyles, are causing a worrying increase in chronic diseases in many developing countries. In Nigeria, for instance, President Olusegun Obasanjo has said: "AIDS, malaria, tuberculosis and

maternal health problems cost our nation dearly. It is less well known that diseases such as heart disease, stroke, cancer and diabetes already have a significant impact and that by 2015 chronic diseases will be a leading cause of mortality in Nigeria."

It is also relatively little known that diabetes today is a bigger killer than AIDS (Financial Times, May 2004) and that by far the largest number of people with diabetes live in poor or developing countries.

An Epidemic Unfolds

The first description of diabetes dates from 1500 BC, when an Egyptian doctor described it as the passing of too much urine. The papyrus was discovered more than 3000 years later, in 1872, by the German academic Georg Ebers. It also suggested that the disease should be treated by changes in diet, one of the oldest forms of therapies still valid today.

While diabetes has been known for millennia, it is only recently that the number of people with diabetes has increased dramatically. In one generation, diabetes has increased sixfold: In 1985 there were an estimated 30 million people with diabetes. In 2007 the disease will affect more than 230 million, and cost societies between $215 billion and $375 billion in medical care.

The triggers for this sharp increase are more sedentary lifestyles and increasing average age, combined with an overconsumption of calories relative to the needs of the body. Thus, the dramatic increase in the number of people with type 2 diabetes (who make up 95 per cent of all cases of the condition) closely follows an increase in average body mass index. The physiological and genetic reasons behind this phenomenon among prosperous as well as poor people may be that the human body is not able to handle long periods of exposure to an excess amount of calories (Diamond, 2003). So it responds by accumulating calories as stored fat in preparation for leaner times.

This makes sense from an evolutionary point of view, as early humans had to prepare for the inevitability of starvation. But this is not the norm now. In both the developed and the developing world, people often have too many and rarely too few calories. Obesity is the result, and with it all

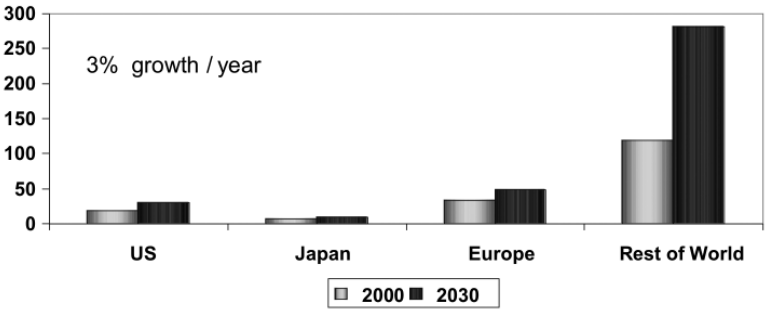


Figure 1. Diabetes-an unfolding epidemic. 370 million people with diabetes by 2030
Source: WHO, January 2003 - Adopted after NN IR

too often comes type 2 diabetes. The consequences are scary: diabetes has become a pandemic.

The large majority of new cases of diabetes will occur in the developing world. This on the one hand shows that diabetes is not a 'disease of the rich', and on the other hand creates the frightening prospect of millions of poor people needing medicine and treatment they hardly can afford. Diabetes has become a public health problem of vast proportions in rich and poor nations alike.

Figure 2 shows the 10 countries with the largest numbers of people with diabetes. In India and China, eight and three per cent of the adult population, respectively, is now affected by diabetes. And the numbers are growing.

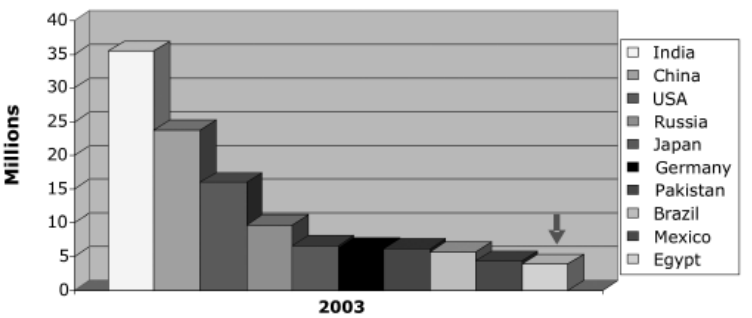


Figure 2. Persons with Diabetes. Top 10 Countries in Numbers
Source: Diabetes Atlas, 2003, 2nd edition

Diabetes in the Arab world

We have seen how diabetes is a serious and growing burden in almost every country in the world. But there are important differences in how the disease has emerged in individual countries and regions. Excluding the tiny states of Nauru and Tonga, four Arab countries are number 1, 2, 3 and 6 on this global list.

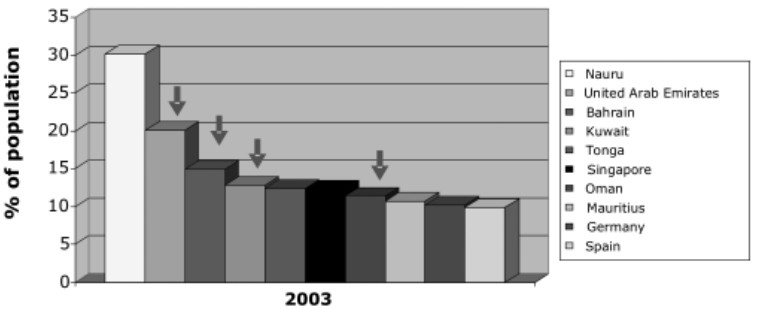


Figure 3. Persons with Diabetes. Top 10 Countries in prevalence
Source: Diabetes Atlas, 2003, 2nd edition

Diabetes in the Arab world has, already today, become a huge public health problem with a prevalence of 10 per cent among all 35-year-olds, and 35 per cent of all 65-year-olds. (Assaad-Khalil, 2006). And this is only the tip of the iceberg. Nearly one Saudi Arabian in five beyond the age of 30 has diabetes. Given that diabetes is a chronic disease of largely middle-aged and elderly people, the future in many countries could be a grim prospect as young populations begin to age (Alzaid, 2006).

In Egypt, 60 per cent of a population of 70 million is under the age of 20, but some 7 million Egyptians have diabetes. Despite this high number, the country has not got to grips with the implications of this disease. A 1997 survey (Assaad-Khalil, 2006) on the attitudes of 1600 young patients revealed that:

- Fewer than two per cent of these patients or their parents attended any educational activity on diabetes outside the consultation setting.
- 82 per cent believed their disease was temporary.

- 52 per cent did not know how to adjust insulin dosage.
- 98 per cent considered that the disease was a barrier against success.
- 46 per cent felt that control of diabetes deprived them of a good life.

These disturbing figures, which most likely find their equivalents in some other countries, emphasize the need for information and education, not only for people with diabetes, but also for their relatives and healthcare professionals.

A Silent Killer

Diabetes is the fifth leading cause of death in the world. The figures for the number of people who die from the disease every year are 3.2 million -- that is, six deaths every minute, according to the World Health Organization (WHO). It is called the silent killer because often it is diagnosed too late, when the damage has already been done.

The fact that 40,000 limbs are amputated every year in India due to diabetes is just one example of the severe, and to a large extent avoidable, damage done when diabetes is not diagnosed and treated in time. This also explains why hospital care makes the largest contribution to direct costs, while medication is a relatively minor expense.

In short, the cost of not treating diabetes is much greater than the cost of proper treatment. Such treatment involves not just medication, but also education. Proper treatment should not be seen as a cost but as an investment in health capital.

Novo Nordisk, the healthcare company specializing in diabetes, and two Danish universities have examined the economic impact of diabetes on Danish and Bangladeshi society. In both cases, the study shows that it pays to invest in better diabetes care. In both countries, the increased productive capacity of people and additional years of life that resulted more than outweighed the investment in improved treatment. When these additional years were adjusted for quality of life, the gains were even more significant.

Declaring War on Diabetes

Over the next two decades, 19,000 people *a day* will develop diabetes. This shocking fact, and the consequences for societies rich and poor, is increasingly recognized by governments and organizations all over the world as a pressing reason to declare war on diabetes.

The European Parliament answered the call by passing a declaration on 16 April 2006 calling for the EU to prioritize diabetes in its health strategies. In June 2006 the EU Council of Health Ministers adopted conclusions on diabetes, recognising the disease as one of the major causes of premature death and reduced quality of life for EU citizens. The Council acknowledged the need for a long-term approach to address and reduce suffering from diabetes and invited EU Member States and the European Commission to take measures in the area of prevention, diagnosis and control of diabetes.

The European Parliament also asked the EC to increase its research efforts in diabetes which are currently lagging dramatically behind those of the US, (Halban, 2006). EU health ministers also invited the EC to support European diabetes research in basic and clinical science and to ensure the wide dissemination of the results of this research.

Novo Nordisk's ambition is to get diabetes on the UN health agenda. To this end, it has joined the International Diabetes Federation and other

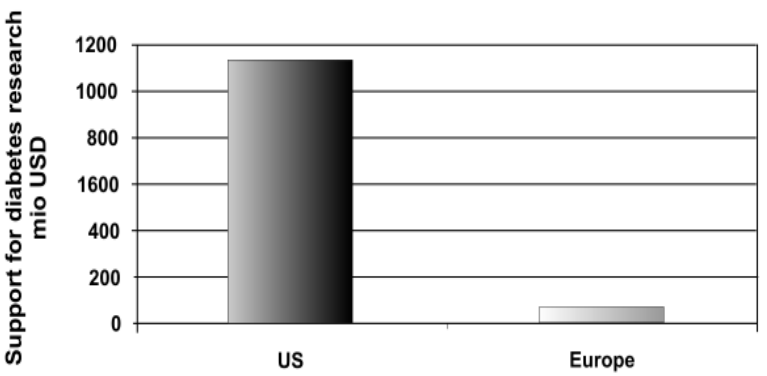


Figure 4. Diabetes Research
Source: Philippe A. Halban, Ele Ferrannini & Jørn Nerup
In: Nature Medicine, January 2006

stakeholders in the campaign for a UN resolution on diabetes to effect lasting political change and show that industry, by taking leadership, can influence science and research, education, and government as well as public policy worldwide to change the lives of people with or at risk of getting diabetes.

The Need for Public Education

"Modern treatment of diabetes does not only lie in the provision of pancreatic transplant services or availability of sophisticated insulin devices and pumps; patient education remains the heart and soul of diabetes care. Education of the patient and his/her family forms the best and most effective way to treat diabetes and prevent long-term diabetic complications. With no magic cure for diabetes in sight, we should consider investing heavily and in a long-term fashion in patient education as the best prescription for diabetes" (Alzaid, 2006).

As a socially responsible company, Novo Nordisk is committed to helping educate people with diabetes and their families as well as healthcare professionals and public stakeholders to improve the lives of people with diabetes and prevent or delay the onset or aggravation of diabetes. Accordingly, the company and partners have launched many activities in 46 countries with one or more of the following goals:

- Creating global health campaigns focused on diabetes.
- Supporting the creation of national diabetes strategies.
- Supporting public awareness programmes on diabetes.
- Supporting education programs for healthcare professionals and people with diabetes.
- Funding or building diabetes clinics.

Novo Nordisk has helped to educate 83,000 healthcare professionals in 20 countries, 50,000 of them in developing countries. Some 226,000 people in 29 countries — 103,000 of them from developing nations — have been directly educated or treated.

As part of its World Partner Program, Novo Nordisk is collaborating with eight developing countries to improve diabetes care by establishing diabetes clinics, training doctors and nurses, and collaborating with governments to set up national diabetes programmes. For example, to tackle

the massive challenge represented by 20 million Chinese with diabetes, the Chinese Ministry of Health, in collaboration with Novo Nordisk and the World Diabetes Foundation, established a Diabetes Management Project with 31 centres for diabetes care covering 300 cities.

For Novo Nordisk, the guiding principle is that information and education will lead to more awareness, early detection and better treatment — which together will promote a healthy lifestyle that could change the face of diabetes.

Conclusion

Novo Nordisk is committed to ensuring greater access to health. The company's approach is built on the four priorities of the WHO. The aim is to partner key stakeholders to develop entirely new strategies and solutions for how to better meet the needs of people with, or who are at risk of developing, diabetes. The economic burden of diabetes, already enormous, will increase in the future if nothing is done. As part of its strategy for access to health, Novo Nordisk undertakes socioeconomic studies to better understand what it takes to change societies, and how the company can contribute to such change.

Novo Nordisk's studies show that poor control of diabetes translates into lost lives, lost quality of life and lost national productivity. With proper treatment, people with diabetes can lead an almost normal life and reduce the risk of disability and premature death.

Seven out of 10 countries with the highest number of people living with diabetes are in the developing world and in 2025, 80 per cent of all cases of diabetes will occur in low and middle-income countries. Obviously, diabetes is not confined to the developed world.

Recognizing the particular needs and conditions in poorer countries, Novo Nordisk is working with partners in seven developing countries to improve diabetes care through activities such as establishing diabetes clinics, training doctors and nurses, and working with governments to set up national diabetes programmes. These countries are Bangladesh, Costa Rica, El Salvador, India, Malaysia, Tanzania and Zambia.

Novo Nordisk offers human insulin to the public health systems in the 50 least developed countries as defined by the UN, at prices not to exceed 20 per cent of the average price in North America, Europe and Japan.

The World Diabetes Foundation (WDF) was launched in 2002 as an independent non-profit organization with an initial grant from Novo Nordisk of $90 million to improve diabetes care and prevention in the world's poorest countries. Today, WDF supports 57 projects with an estimated direct impact on 24 million people in more than 65 countries in the developing world.

By working together with other stakeholders, industry can change diabetes and therefore change the lives of millions of people.

References

1. Diamond, J., 2003. Nature 423, pp 599-602
2. Assaad-Khalil, S.H., 2006. 'Diabetes in the Arab World'.
3. Halban, P. A., Ferrannini, E. and Nerup, J., 2006. Nature Medicine 12, pp 70-71
4. 'The Global Economic Cost of Diabetes Mellitus', Report of Findings, Boston Health Economics, Inc., January 2003.

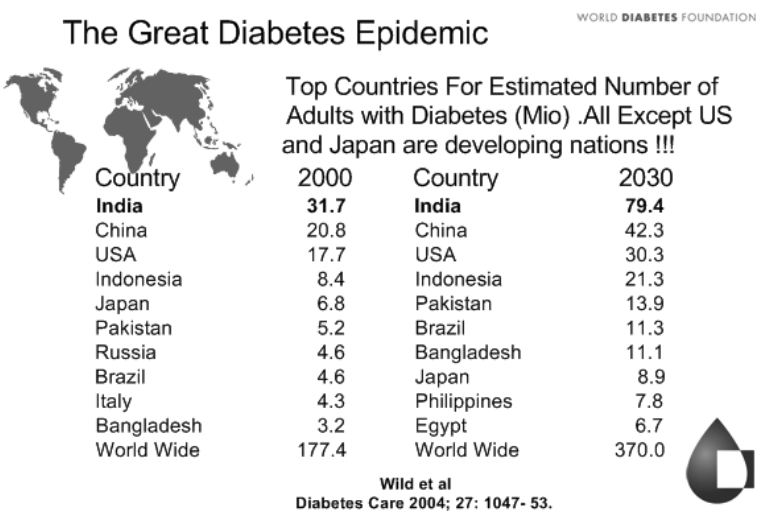
27

Dealing With the Burden of Diabetes in Developing Countries

Anil Kapur

Introduction

Diabetes is becoming a major public health problem globally but will impact the developing world much more severely due to lack of resources and preventive public health initiatives. Earlier diagnosis and early institution of proper routine care of diabetes is not costly; delayed diagnosis and delayed and improper routine care is very costly. There is an urgent need for a multi-sectoral approach in which governments, NGOs, the health industry, national associations, healthcare providers and people with diabetes can play a role in providing at least minimum standards of care that would help those affected maintain the best possible quality of life. The World Diabetes Foundation (WDF) aims to address and potentially limit the epidemic by bringing diabetes higher on the global health care agenda as well as fund sustainable projects in awareness, primary prevention, building healthcare capacity, and improving access to care in the poorest countries. Many of its 72 ongoing projects are already achieving these objectives.



Diabetes is a Major Problem in the Developing World

Diabetes is rapidly emerging as a major health care problem in the developing world especially in urban areas. The rapid increase in population and increased longevity, coupled with rapid urbanization and changes from traditional lifestyles (due to increased economic activity) is causing a diabetes pandemic.

According to the data from the International diabetes Federation diabetes already afflicts 230 million people in the world and the numbers are growing rapidly. WHO estimates that by 2030 the number is likely to exceed 370 million. Seven out of the top ten countries with diabetes are in the developing world and 80 per cent of people with diabetes in a few years will be living in poor and middle-income countries. Every 10 seconds one person dies due to diabetes related complications (3 million/year) and in the same ten seconds two new people develop diabetes (6 million/year). Diabetes is a major cause of limb amputations, is the leading cause of acquired blindness in the developed world and rapidly emerging as one of the leading causes of blindness in the developing world as well.

Diabetes affects the urban poor as much as the middle and upper income people everywhere in the world. In poorer countries, people living below the poverty line tend to be diagnosed later; have less access

to treatment and as a result suffer more acute and late complications as compared to the rich.

People with diabetes use higher health care resources. The excess cost is related directly to higher cost of treating late complications and indirectly to the economic loss due to lost man-days and economic opportunity. In the absence of health insurance and a significant or credible social security system to fall back on during illness or bad times, an illness affecting the earning or active member of the family, affects not only this individual but often has significant effect on others in the family as well. It may force other normally non-working members to start work, often prematurely at lower wages, cut short children's education with its long-term financial consequence for them and the family.

The prevailing poverty, ignorance, illiteracy and poor health consciousness further adds to the problem. Many sociological factors determine long-term outcome of chronic illnesses. A study of these factors and their influence on the prognosis and outcome are necessary to tackle diabetes in the community. There is emerging evidence that diabetes education, awareness and improved motivation for self care improves care, reduces complications and may thus reduce overall economic costs of diabetes.

Why is Diabetes Increasing?

Rapid technological strides and globalization of the world is bringing about significant changes in the way we live and work. Societies and economies in rapid transition show these changes most visibly; here lifestyles and culture are quickly catching up with the changing landscapes and new economic realities. All over the world, traditional lifestyles and dietary patterns that sustained people over generations are disappearing. The traditional nutritious diets are being replaced by poor quality highly processed food that contains more fat, salt, sugar, oil and meat. As people move up the economic ladder their eating patterns change from subsistence to more luxury items. Food processing is growing rapidly. The growth in the consumption of calorie dense processed foods has been paralleled by a decrease in exercise. The result of this is increasing problems of weight

and obesity. A study from rural India shows that, over 14 years, diabetes had increased from 2.2 per cent to 6.4 per cent of the population and that this had been accompanied by increases in such factors as regular use of motorized transport, nearby water supply and watching television regularly.

Human metabolism programmed to a life style of hunter-gatherer (fasting and feasting) enabled us survive tough times but is unable to cope with modern living conditions, with its too little activity and too much (refined) food to eat (constant feasting). The tissues that store food energy (muscles, liver and fat) depend on insulin to help them achieve this. When the human body is exposed to food oversupply (overeating and/or less physical activity) these tissues protect themselves from being inundated by the excess food energy by developing insulin insensitivity (resistance). As a consequence, this is compensated initially by the insulin producing β-cells, secreting more insulin to drive the excess nutrients into the tissues, resulting in a new equilibrium where there is a relative excess of insulin, excess nutrient stores (fat depots) and normal blood sugar. The excess insulin production continues over time as long as the β-cells can produce increasingly large amounts of insulin in response to the continuing overeating and little physical activity. When de-compensation sets in, it initially manifests as a rise in post meal glucose level (IGT) and subsequently diabetes. This typifies the classical overweight person with diabetes.

Another, explanation for this epidemic rise is that people programmed at birth or early childhood to survive in a nutritional deficient state (malnutrition in the mother during pregnancy or early childhood malnutrition associated with a previous lower standard of living), when exposed to nutritional excess in adult life, (now associated with an improved living standard or urban migration) are unable to cope with it. As a self-preserving mechanism the tissues counteract this (over) nourishment by developing insulin insensitivity as explained above. On the other hand, the smaller and fewer β-cells (programmed for a smaller body size) fail earlier — resulting in type 2 diabetes without the person being too overweight.

In others, the stress of urban living or urban migration may unmask a genetic predisposition to β-cell failure. Undue psychological, emotional or physical stress leads to liberation of an excess amount of stress

hormones that oppose the effects of insulin. While stress adds to the above mechanisms, it may act on its own as well.

These reasons are often cited to explain the high prevalence of diabetes amongst migrant populations and also the rising prevalence in urban areas of developing economies worldwide.

Access to Care, Complications and Cost of Care

Over the last 30 years type 2 diabetes has changed from being seen as a relatively mild ailment associated with aging and the elderly ('just a touch of sugar') to one of the major contemporary causes of premature mortality and morbidity in most countries. Through its effects on cardiovascular disease (70-80 per cent of people with diabetes die of cardiovascular disease) it is now one of the leading causes of death. Complications due to vascular (micro / macro) and neurological disease are the main cause of morbidity and mortality amongst persons with diabetes. Bacterial and fungal infections are common. Tuberculosis of the respiratory tract and other tissues, fungal infections of the skin and mucous membranes, bacterial infections of the urinary tract, and deep tissues pose a health hazard for persons with diabetes.

People with diabetes are considered to carry a two-to-four fold risk of coronary heart disease. Risk of developing end stage renal disease (ESRD) in type 2 diabetes is 17 fold. Worldwide, diabetes is the leading cause of ESRD, requiring dialysis or transplantation. Diabetic retinopathy is the leading cause of blindness and visual disability in the economically developing as well developed societies. Sixty per cent of type 2 diabetes patients will develop retinopathy at some time if they survive long enough. Diabetic foot is the most common cause of prolonged hospitalization and accounts for half of all non-traumatic amputations. Prevention is possible by simple means — in countries that have introduced specific foot programs, the incidence of foot problems have fallen by half.

The World Health Organization (WHO) estimates that 40 per cent of people with diabetes need oral medications and 40 per cent need insulin injections. However, it is estimated that only a small fraction of people with diabetes in the developing countries are being treated. There is a great disparity between expenditure on communicable diseases and non-

communicable diseases such as diabetes. The official overseas development aid to the health sector in 2002 was approx. $2.9 billion of which only 0.1 per cent is allocated to chronic diseases. Indeed, diseases such as HIV/Aids have traditionally taken up most of the focus and resources. But WHO predicts that non-communicable diseases such as diabetes will become the world's main cause of disability and death during the next 25 years and in 2005, 35 million people will die from these: more than the number of deaths from all infectious diseases (including HIV/AIDS, tuberculosis and malaria). The developing countries carried 90 per cent of the world's total disease burden, yet they benefited from only 10per cent of global health resources. Indeed WHO estimates that one third of the world population lack regular access to essential drugs, and this figure is expected to rise to over 50per cent in the least developed parts of Africa and Asia.

Our studies show that the less educated, unemployed people, especially those living in semi urban or rural areas who cannot afford or do not have access to even bare minimum health care, are likely to be diagnosed late, and likely to develop or have at presentation, diabetes related complications. This has remarkable socioeconomic significance: those who will need more advanced / more expensive care for diabetes related complications, are often the ones who can ill afford such care. While some of these unfortunate people may still be able to afford routine care, when burdened with complications requiring advanced expensive care, it would be like the proverbial last straw that broke the camel's backs and drives many of them to borrow and enter the debt trap with disastrous consequences to the individual and society.

Delayed diagnosis and untreated or improperly managed diabetes leads to complications. Complications requiring multiple therapies and prolonged hospitalization are responsible for most diabetes related direct costs. Amongst patients hospitalized, the average annual direct costs are more than double of those not hospitalized. Complications are also responsible for indirect costs in terms of productivity loss and absenteeism.

In the CODE-2 study (Cost of Diabetes type 2 in Europe) compared to people with no complications, the cost in people with micro vascular complication was 1.7X. With macro vascular complication, 2.0X and both together, 3.5X. Similar findings were noted in the CODI Study where increasing number of complications increased annual cost of care. The mean direct cost per person with type 2 diabetes (including hospitalisation)

averaged $149 but if indirect costs are added, the total annual cost averaged $415.

Early diagnosis and proper control prevent, retard or arrest development of complications both in type 1 and type 2 diabetes. Effective intervention means prevention and prevention means primary prevention — life style changes, and secondary prevention — reducing the burden of complications by early diagnosis and proper care.

Each of us involved in diabetes care needs to be aware of what drives cost. Earlier diagnosis and early institution of proper routine care of diabetes is not costly; delayed diagnosis and delayed and improper routine care is very costly.

There is an urgent need for a multi sectoral approach in which governments, NGOs, the health industry, national associations, healthcare providers and people with diabetes can play a role in providing at least minimum standards of care that would help those affected maintain the best possible quality of life. This is precisely what the World Diabetes Foundation (WDF) is aiming for.

The Work of the World Diabetes Foundation

The World Diabetes Foundation (WDF) aims to address and potentially limit the diabetes epidemic by bringing diabetes higher on the global health care agenda as well as fund sustainable projects in awareness, primary prevention, building healthcare capacity, and improving access to care in the poorest countries. The World Diabetes Foundation acts as a catalyst to build sustainable relations between different stakeholders ensuring the individual project initiatives live on even after the specific project funding has ceased.

The World Diabetes Foundation focuses on the following areas:

- Awareness about diabetes
- Prevention of diabetes and complications
- Education and training for people with diabetes and health care professionals
- Access to essential medicines in diabetes
- Detection, treatment and monitoring of diabetes

It is very important to the World Diabetes Foundation that its funds are directed to people with the greatest burden and most need: namely for diabetes projects in the developing countries. The strategy is to act as a catalyst — help others do more — making a much greater impact than the Foundation's size would suggest. The WDF seeks partnerships with established organizations in the areas of health, diabetes and development aid to build on existing structure and resources that help bring diabetes higher on the global health care agenda. Through these partnerships we aim to raise global awareness of diabetes and help find the resources to address and potentially limit the epidemic.

The WDF has established project related partnerships with organizations like WHO, IDF and DANIDA, The Insulin Foundation, the German NGO Humanitäre CubaHilfe, the Spanish foundation Fundación para la Diabetes, local diabetes associations and ministries of health in various countries, leading diabetes research institutions and WHO collaborating centers.

WDF was established in 2002 as an independent trust and is governed by a board of six experts in the field of diabetes, access to health and development assistance.

The Foundation is currently chaired by Pierre Lefebvre, who is also the President of the International Diabetes Federation. The foundation already supports 72 projects in more than 65 developing countries. These projects in the coming three-to-four years will potentially influence the diabetes treatment of 26 million people directly in the developing countries. Although established through a commitment of 500 million Danish Kroners over ten years by Novo Nordisk A/S, (which guarantees continued resources for the Foundation's work) WDF raises funds from other sources as well to support specific projects ensuring a multiplier effect; The current project portfolio is worth $80 million of which the WDF will contribute only $22 million. Thus for every dollar the foundation spends it is able to attract three dollars in cash or kind from other sources.

For information on the World Diabetes Foundation and WDF funded projects please visit: www.worlddiabetesfoundation.org

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India's Diabetes Epidemic

Vishwanathan Mohan

Introduction

The first authentic data on diabetes in the Indian subcontinent was the multi-centre epidemiological study carried out by the Indian Council of Medical Research (ICMR) in the 1970s. According to this study, the prevalence of diabetes was 2.1 per cent in India's urban areas and 1.5 per cent in rural areas (Ahuja, 1979). Subsequently, a series of studies have documented the rising trend of diabetes in India's cities and countryside (Ramachandran et al., 2001; Misra, 2001; Kutty, 2000; Patel, 1986; Murthy, 1984). However, it is difficult to compare trends across these studies due to different sampling frames, varying degrees of urbanization and variations in the methods used.

The southern city of Chennai, the fourth largest in India, is one of the few regions where well-conducted epidemiological studies on the prevalence of diabetes, using the same diagnostic criteria, have been repeatedly performed. The Chennai Urban Rural Epidemiology Study (CURES), conducted in 2001 on a representative population of the city, provided the opportunity to compare trends in the prevalence of diabetes in Chennai over the last two decades. The overall crude prevalence shown by this study was 15.5 per cent, which included 6.1 per cent self-reported diabetics and 9.4 per cent previously undiagnosed diabetics. The prevalence of diabetes increased by 39.8 per cent from 1989 to 1995, and 16.3 per cent in the next five years. It then rose by 6.0 per cent in the following four years. So within a span of 14 years, the prevalence of diabetes had

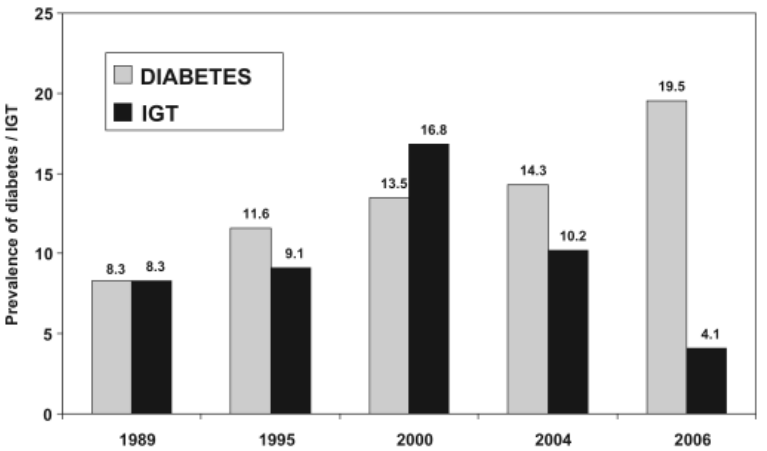

Figure 1. Prevalence of Diabetes and IGT in India

increased by 72.3 per cent. This rise is further supported by a recent study from Kerala, the Amrita Diabetes and Endocrine Population Survey (ADEPS), which documents the prevalence of diabetes as 19.5 per cent (Menon et al., 2006).

The rates of diabetes in rural India have consistently remained about 50 per cent lower than in cities. However, the growth trend in rural areas appears to parallel that of urban areas. The 1970s ICMR study indicated that the incidence of diabetes in rural India was around 1.5 per cent. In the 1980s, a study conducted in the rural population of Eluru, south India (Rao et al., 1989) reported a prevalence rate of 1.6 per cent. A recent study comparing shifts in the incidence of diabetes in rural India over time recorded a significant increase, up to 6.36 per cent in 2003 (Ramachandran et al., 2004).

While diabetes is on the rise, there is good news. The prevalence of the blood sugar disorder (and sometime precursor of diabetes) impaired glucose tolerance now appears to be decreasing. In India's cities, IGT incidence rose by 9.6 per cent from 1989 to 1995 and by 84.6 per cent from 1995 to 2000. However, it decreased by 39.3 per cent from 2000 to 2004 (Mohan et al.; Misra, 2001). Similar results were obtained in the ADEPS study, which showed a prevalence of 4.2 per cent (Menon et al., 2006) (Figure 1).

According to a World Health Organization study, India today has more diabetics than any other country. Estimates run at 32 million people — a figure expected to rise to 79.4 million by the year 2030 (one-sixth of the world total) (Wild et al., 2004).

The NCD Risk Factor Study

The NCD (non-communicable disease) risk factor surveillance study was a collaboration between the WHO and the ICMR. Its goal was to develop a sustainable system for NCD surveillance in India. Conducted in five different states representing different geographical locations (East, south, west and central India), it involved 39,429 people aged 15 to 64, with 12,732 from cities, 13,170 from urban slums, and 13,525 from rural areas. The methodology was adapted from the WHO Global STEPwise approach for risk factor surveillance for NCDs.

Overall, the figure for self-reported diabetes was 4.4 per cent. The lowest prevalence was recorded in rural areas, and the highest in cities (ICMR, 2000). Previous studies have shown that for every diagnosed case of diabetes, there is one undiagnosed case (Mohan et al.; Ramachandran et al., 2001), and taking these into account would mean that the prevalence of overall diabetes in India would be 8.8 per cent. The adult population of India in the 2001 census was about 562 million, and assuming an eight per cent prevalence of diabetes, that would mean that 44 million individuals would have been affected by diabetes in 2001.

Factors Driving Diabetes in India

The Asian Indian phenotype

It has been well documented that Asian Indians have certain unique clinical and biochemical characteristics that are collectively called the Asian Indian phenotype. Despite lower rates of obesity as defined by body mass index (that is, weight in kilogrammes/height in square metres), Asian Indians tend to have larger waist measurements and waist-to-hip ratios and thus have a greater degree of central body obesity and increased visceral fat (Anjana et al., 2004). This distribution of body fat is associated with a

metabolic profile characterized by higher plasma insulin levels (Mohan et al., 1986), a greater degree of insulin resistance as measured by glucose clamp studies (Laws et al., 1994), and a higher prevalence of diabetes (McKeigue et al., 1991) and premature coronary artery disease (McKeigue et al., 1989).

Healthier babies, older populations

India is the second largest country in the world, with a population of more than one billion. Advancements in medical technologies and care have boosted lifespan from 49 to 64 between 1970 and 2003. There have also been dramatic decreases in infant mortality rates. Today, eight per cent of the population is over 60 and this is expected to increase by 11 per cent by 2021. This demographic shift of a growing elderly population is likely to dramatically increase rates of diabetes in India over the next few decades.

The rise in 'affluenza'

Presently, 35 per cent of India is urbanized in contrast to 15 per cent in the 1950s. The proportion of the population living in cities has increased by 2.1 per cent over the decade from 1991 to 2001. We have seen how diabetes tends to hit more people in cities than in rural areas. But there is more to the story. Recently, studies have also shown that with affluence, the prevalence of diabetes tends to rise (Mohan et al., 2001). Affluence tends to lead to a more sedentary lifestyle and higher fat and calorie consumption in developing countries, all factors leading to an increase in diabetes cases. This is precisely the opposite of what is seen in the west, where poorer populations tend to eat fattier, more sugary diets and take less exercise, and thus are more at risk of developing diabetes.

Most of the urban surveys in India have indicated low levels of physical activity among 50 to 60 per cent of residents. In the Chennai Urban Population Study (CUPS), only 6.2 per cent of adults admitted to doing any kind of exercise more than three times a week (Mohan et al., 2005). A linear graded relationship was observed between physical inactivity and diabetes among the Chennai residents studied, with diabetes higher among those engaging in light exercise (17 per cent) compared to moderate (9.7 per cent) and heavy (5.6 per cent).

Diabetes Prevention in India

As India is now facing an epidemic of diabetes, the time has come to actively prevent diabetes in the community. This can be achieved through the following strategy.

Identifying high-risk subjects

Based on a recent population based study, we have developed a risk score called the Indian Diabetes Risk Score (IDRS) (Mohan et al., 2005). This score was derived using four simple parameters: age, abdominal obesity, family history and physical activity. The IDRS is a cost-effective tool for screening diabetes, as it demands minimum time and effort. A cut-off score of ≥ 60 was derived to detect undiagnosed diabetes based on optimum sensitivity and specificity. It was further observed that subjects with normal glucose tolerance and an IDRS value of ≥ 60 had increased levels of all cardiovascular risk factors and the pre-diabetic condition metabolic syndrome (Mohan et al., Diabetes, Obesity and Metabolism, 2006 [in press]). So people with have high scores, regardless of blood sugar status, could be advised to modify their lifestyles, as these are risk factors not only for diabetes but also for cardiovascular disease.

Increasing awareness in the community

The CURES study revealed that only 75 per cent of Chennai residents knew that a disease called diabetes existed; only 12 per cent were aware that obesity and physical inactivity could increase the risk of developing diabetes; and only 25 per cent felt diabetes is preventable despite mass educational programmes organized by tertiary care centres (Deepa et al., 2005). This data clearly emphasizes the need for mass diabetes education programmes in both urban and rural India.

Encouraging lifestyle changes

Studies have consistently demonstrated that lifestyle changes can prevent diabetes (Knowler et al., 2002). The community has to be motivated to adapt healthier lifestyles. As a follow-up of the CUPS study, we persuaded

♂ Men		♀ Women	
Waist circumference:		***Waist circumference:***	
< 80 cm	0	<90 cm	0
≥80-89 cm	10	≥90-99 cm	10
≥90 cm	20	≥100 cm	20

Age:	
<35 years	0
35–49 years	20
≥50 years	30
Physical activity:	
Moderate to Vigorous exercise [regular] or strenuous [manual] work at home / work	0
Light exercise [regular] or light physical activity at home / work	20
No exercise and sedentary activities at home / work	30
Family history of diabetes:	
No diabetes in parents	0
One parent is diabetic	10
Both parents are diabetic	20

Score total	Risk
<30	**Low risk**
30-<60	**Moderate risk**
≥60	**High risk**

Figure 2. Indian Diabetes Risk Score (IDRS)

the residents of one residential area to construct a public park, which significantly changed the level of physical activity level in this community (WHO, 2005). This led to the construction of several new parks in neighboring areas, and the government responded by adding 200 parks in the city.

Based on the CUPS success story, we planned a massive awareness and prevention programme called Prevention, Awareness, Evaluation and Counseling (PACE) Diabetes project (Suresh et al., 2005). This project has three phases. In the first, mass awareness camps are being conducted to send information on diabetes to over a million people. Phase 2 involves screening nearly 200,000 people for diabetes. And in the third phase, the prevention of diabetes will be undertaken at the community level using lifestyle intervention strategies. The project is expected to increase diabetes awareness at the community level and also to help to formulate a strategy for preventing diabetes.

Conclusion

India's current diabetes epidemic, spurred on by urbanization and lifestyle shifts, could have a serious impact on the nation's health. There is thus a need to advocate adequate prevention measures. These should target lifestyle changes: adopting healthier dietary choices, boosting physical activity and reducing stress. Such a strategy could lead to a significant reduction in India's health burden from diabetes in the future.

References

1. Ahuja, M.M.S. 1979. 'Epidemiology studies on diabetes mellitus in India'. In Ahuja, MMS (ed). Epidemiology of diabetes in developing countries Interprint, New Delhi, India, pp 29-38.
2. Anjana, M. et al*.,* 2004. 'Visceral and central abdominal fat and anthropometry in relation to diabetes in Asian Indians' Diabetes Care27; pp 2948-2953
3. Beckles, G.L. et al*.,* 1986. 'High total and cardiovascular mortality in adults of Indian descent in Trinidad unexplained by major coronary risk factors' The Lancet 1, pp 1298-1301.
4. Cheah J.S. et al., 1985. 'Epidemiology of diabetes mellitus in Singapore: comparison with other ASEAN countries' Ann Acad Med Singapore 14; pp 232-239.
5. Deepa, M. et al., 2005. 'Awareness and knowledge of diabetes in Chennai — the Chennai Urban Rural Epidemiology Study' (CURES – 10). Journal of the Association of Physicians of India 53; pp 283-287.
6. Dowse, G.K. et al., 1990. 'The high prevalence of non-insulin-dependent diabetes and impaired glucose tolerance in Indian, Creole and Chinese Mauritians'. Mauritius Noncommunicable Disease Study Group. Diabetes 39; pp 390-396.
7. ICMR. 2005. 'Risk factor surveillance for non-communicable diseases (NCDs): the multi-site ICMR-WHO collaborative initiative'. Available at: www.globalforumhealth.org/filesupld/forum9/CDper cent20Forumper cent209/papers/Shahper cent20B.pdf.
8. NCD risk factor surveillance study — Chennai chapter, Indian Non-communicable Diseases Network. Available at www.ncd.in/downloads/CHENNAIper cent20Chapter.pdf.
9. Knowler, W.C. et al., 2002. 'Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin'. New England Journal of Medicine 346; pp 393-403.
10. Kutty, V.R. et al., 2000. 'Type 2 diabetes in southern Kerala: variation in prevalence among geographic divisions within a region'. National Medical Journal of India 13; pp 287–292.

11. Laws, A. et al., 1994. 'Resistance to insulin-stimulated glucose uptake and dyslipidemia in Asian Indians'. Arteriosclerosis, Thrombosis and Vascular Biology 14; pp 917-922.
12. Mather, H.M., Keen, H. 1985. 'Southall Diabetes Survey: prevalence of known diabetes'. British Medical Journal 291; pp 1081-1084.
13. McKeigue, P.M., Miller, G.J., Marmot, M.G., 1989. 'Coronary heart disease in south Asians overseas: a review'. Journal of Clinical Epidemiology 42, pp 597-609.
14. McKeigue, P.M., Shah, B., Marmot, M.G. 1991. 'Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians'. *The Lancet* 337; pp 382-386.
15. Menon, V.U. et al., 2006 'Prevalence of known and undetected diabetes and associated risk factors in central Kerala' — ADEPS. Diabetes Research and Clinical Practice.
16. Misra, A. et al., 2001. 'High prevalence of diabetes, obesity and dyslipidaemia in urban slum population in northern India'. International Journal of Obesity and Related Metabolic Disorders 25; pp 1722–1729.
17. Mohan, V. et al., 1986. 'Serum immunoreactive insulin responses to a glucose load in Asian Indian and European Type 2 (non-insulin dependant) diabetic patients and control subjects'. Diabetologia 29, pp 235-237.
18. Mohan, V. et al., 2001. 'Intra urban differences in the prevalence of the metabolic syndrome in southern India — the Chennai Urban Population Study (CUPS-4)'. Diabetic Medicine 18, pp 280 –287.
19. Mohan, V. et al*.,* 2005. 'Association of physical inactivity with components of metabolic syndrome and coronary artery disease — the Chennai Urban Population Study (CUPS no. 15)'. Diabetic Medicine 22; pp 1206 – 1211.
20. Mohan, V. et al*.,* 2005. 'A simplified Indian Diabetes Risk Score for screening for undiagnosed diabetic subjects'. Journal of the Association of Physicians of India 53; pp 759-763.
21. Mohan, V et al., 2006. 'Secular trends in the prevalence of diabetes and impaired glucose tolerance in urban South India — the Chennai Urban Rural Epidemiology Study (CURES-17)'. Diabetologia 49; pp 1175–1178.
22. Mohan, V. et al., 2006 (in press). 'A diabetes risk score helps identify metabolic syndrome and cardiovascular risk in Indians – The Chennai Urban Rural Epidemiology Study (CURES – 38)'. Diabetes, Obesity and Metabolism.
23. Murthy, P.D., Pullaiah, B., Rao, K.V., 1984. 'Survey for detection of hyperglycaemia and diabetes mellitus in Tenali'. In Bajaj, J.S., ed. Diabetes mellitus in developing countries. Interprint, New Delhi, India, pp 55–60.
24. Omar, M.A. et al., 1985. 'The prevalence of diabetes mellitus in a large group of Indians'. South African Medical Journal 67, pp 924-926.
25. Patel, J.C. 1986. 'Prevalence of hypertension and diabetes mellitus in a rural village'. Journal of the Diabetic Association of India 26; pp 68–73.
26. Ramachandran, A. et al., 1997. 'Rising prevalence of non insulin dependent diabetes in urban populations in India' Diabetologia 40; pp 232–237
27. Ramachandran, A. et al., 2001. 'Diabetes Epidemiology Study Group in India (DESI): high prevalence of diabetes and impaired glucose tolerance in India — National Urban Diabetes Survey' Diabetologia 44; pp 1094-1101.

28. Ramachandran, A. et al., 2004. 'Temporal changes in prevalence of diabetes and impaired glucose tolerance associated with lifestyle transition occurring in the rural population in India' Diabetologia 47; pp 860-865.
29. Ramaiya, K.L., Kodali, V.R.R., Alberti, K.G.M.M. 1991. 'Epidemiology of diabetes in Asians of the Indian sub-continent' International Journal of Diabetes in Developing Countries 2; pp 15-36.
30. Rao, P.V. et al., 1989. 'The Eluru survey: prevalence of known diabetes in a rural Indian population'. Diabetes Research and Clinical Practice 7; pp 29-31.
31. Suresh, S. et al., 2005. 'Large-scale diabetes awareness and prevention in South India'. *Diabetes Voice* 50; pp 11-14.
32. WHO. 2005. 'Improving the built environment in India. Preventing chronic disease: a vital investment'. Bulletin of the World Health Organization, Geneva.
33. Wild, S. et al., 2004. 'Global prevalence of diabetes: estimates for the year 2000 and projections for 2030'. Diabetes Care 27; pp 1047-1053.
34. Zimmet, P. et al., 1983. 'The prevalence of diabetes and impaired glucose tolerance in the biracial (Melanesian and Indian) population of Fiji: a rural-urban comparison'. American Journal of Epidemiology 118; pp 673-688.

29

The Growth of Diabetes in Egypt

Samir Assaad Khalil

Egypt will Face Explosive Growth in Diabetes

Due to a rapidly increasing and ageing population, Egypt will have the largest number of people with diabetes in the region by 2025 (over the age of 20 years (Sicree et al., 2003). Factors driving a rapid increase of the burden of diabetes include population growth, ageing, obesity, consumption of fast food and an increasing sedentary mode of life. An important contributing factor to the burden of obesity in Egypt is negative aspects of modernization/westernization. Pertinent examples include: unemployment, machine driven jobs, higher technology, computers, television, videos, DVDs. This is further aggravated by the absence of places for children to play or for youth and adults to practice any sport.

It is a serious situation because more and more people will suffer from cardiovascular complications such as nephropathy, neuropathy, amputations and retinopathy. On the other hand, one can improve this alarming situation. For this we should empower diabetics to be more active in the management of their disease. Due to a rapidly increasing and ageing population, Egypt will have the largest number of people with diabetes in the region by 2025.

Survey by Arab et al. (1992) reported an overall prevalence of 6.25 per cent in the population aged above 20 years. In urban areas, the prevalence was much higher at 8.93 per cent and lower in the rural areas. One of the

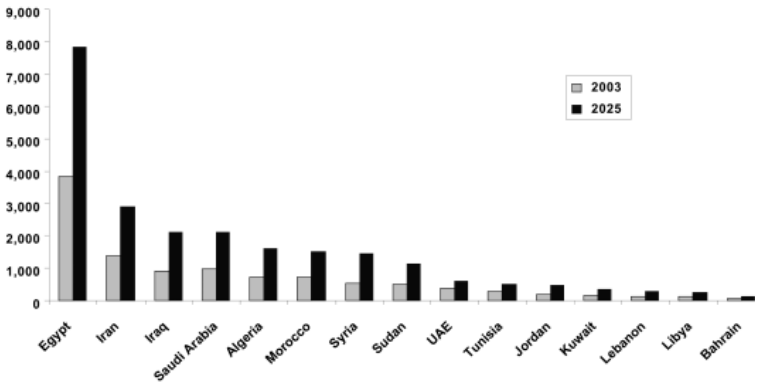

Figure 1. Egypt will face explosive growth of diabetes

peculiarities of this survey was to differentiate between rural agricultural and rural desert areas; the former showed a prevalence of 4.76 per cent and the latter 1.58 per cent.

In Ali et al., the prevalence reported was even more alarming. They reported a prevalence of 9.3 per cent in the Egyptian population as a whole, 4.9 per cent in the rural areas and differentiated the urban areas into areas with high socio-economic class and others with a low socio-economic level. The former showed a prevalence of 20 per cent and the latter of 13.5 per cent. A third survey (Assaad Khalil et al., 2006) has been conducted in Alexandria (4.5 million inhabitants). This is a joint work of the Alexandria Faculty of Medicine, Medical Research Institute, High Institute of Public Health, Alexandria University, Egypt and the Mario Negri Institute, Milan, Italy. This project initiated a regional population based diabetes registry in Alexandria (86,129 patients). Overall prevalence of DM in Alexandria (including all ages) was estimated to be 4.39 per cent with a M:F ratio of 1:1.3. This, when adjusted for age will be very close to the prevalence reported by Arab et al. In this project a sub-sample (3000) from registered cases was chosen proportionally, for the study of the demographic characteristics of patients and complications of diabetes mellitus. When computing the probability of surviving free from complications for 20 years in Alexandria among subjects with T2 DM, alarming figures were obtained.

Table 1. Prevalence of sedentary lifestyle & obesity in the Egyptian population aged ≥ 20 years by residence and socio- economic status (1992-1994)

Residence & Socio-economic Status	Prevalence of Sedentary Lifestyle (per cent)	Prevalence of Obesity (per cent)
Rural	52	16
Urban Lower SES	73	37
Urban Higher SES	89	49
Total	63	27

SES= Socio-economic status

Table 2. The probability of surviving free from complications for 20 years in Alexandria among subjects with T2 DM

For Neuropathy	30.5	per cent
For Nephropathy	66.8	per cent
For Retinopathy	44.6	per cent
For Cardiac Complications	77.9	per cent
For Diabetic Foot	71.5	per cent
For Other Complications	92.0	per cent

Alexandria / Milan Universities Survey (1995-2002)
Complications & Survival Probabilities.

Medical Care and Patient Education in Egypt

Therapeutic patient education is a crucial component of healthcare, yet, despite this fact, about one third of Egyptian subjects with diabetes have never experienced such a service. Moreover, these patients are neither aware nor encouraged to seek medical care in a regular way. Most of these patients do not take an active role in the management of their disease. In fact only 7.8 per cent of patients perform self monitoring of their blood glucose.

Another pertinent feature of the health care activity in our population is the great discrepancy observed in these activities between those who are health insured and those who are not. A striking example is that only 50 per cent of non insured patients have regular follow up visits versus 96.3 per cent of those who are insured.

Table 3. Distribution of diabetic patients according to their activities in seeking medical care

	Total (n=1000)	NHI (n=400)	HI (n=600)	P
	per cent	per cent	per cent	
Regular Follow up Visits	77.8	50.0	96.3	<0.001
Accessibility to Clinic	86.1	77.3	92.0	<0.001
Adherence to Diet Regimen	64.3	51.5	72.8	<0.001
Regular Use of Drugs	88.6	84.9	94.3	<0.001
SMBG	7.8	6.5	8.7	0.211
Testing of Glucosuria at Home	26.2	24.5	27.3	0.318
Light or Moderate Physical Activity	65.2	49.2	75.8	<0.001
Never Smoking	69.4	79.8	62.5	<0.001

HI: Health insured; NHI: Non Health insured; SMBG: Self monitoring of blood glucose

Publications dealing with the cost of diabetes in Egypt are very scarce. The results of a study conducted in Alexandria and published in 1993 by Arab et al. revealed a relatively low cost for the health care (mainly devoted to therapy) because of substantial government subsidies for basic medication. The cost of dialysis was estimated to be $555 per month (10 times the yearly per capita income). The total direct cost of diabetes care in Egypt in 1990 has been estimated to be $74 million equivalent to two-thirds of the total health care budget in that year. Another aspect of the economic burden of diabetes is the indirect cost of the disease. The estimated absenteeism in this study was estimated to be 38.76 days/ patient/ year.

Problems Peculiar to the Developing Countries

In Egypt, as in most developing countries, special situations constitute a barrier for achieving therapeutic targets. These include: the rate of illiteracy which exceeds 40 per cent of the population as a whole and is at more than 50 per cent among women; widespread myths and misconceptions about health and disease among those on low incomes. This is complicated by

Table 4. Distribution of diabetic patients according to their health information and educational intervention

	Total (n=1000)	NHI (n=400)	HI (n=600)	P
	per cent	per cent	per cent	
Having information about:				
Correct diet	82.5	82.3	82.7	0.865
SMBG	16.1	10.3	20.0	<0.001
Dealing with hypoglycemia	77.4	70.5	82.0	<0.001
Foot care	75.7	65.5	82.5	<0.001
Self management of insulin*	56.7	49.6	62.1	0.041
Main source of information:				
Education meeting / Health news	14.6	17.9	12.3	0.280
Physician	82.1	78.8	84.3	
Nurse	3.3	3.3	3.3	
Frequency of health education:				
Never	31.9	54.3	17.0	<0.001
Occasional/regular	68.1	45.7	83.0	

HI: Health insured; NHI: Non Health insured; SMBG: Self monitoring of blood glucose
* Only cases treated with insulin are considered (115 in NHI and 153 in HI) Cost of medical care and economic burden of diabetes in Egypt

poor distribution of the available material, lack of maintenance and socio-cultural barriers (Assaad Khalil, 2005).

Myths and Misconceptions

Regards diet: that water intake should be decreased when passing large amounts of urine. All carbohydrates should be removed from the diet. Honey is good for diabetes control. Consuming bitter and salty foods buffers hypoglycemia. As regards treatment: medications in the form of insulin or oral agents suppress pancreatic activity and cause habituation. Medications should be stopped during acute illness. Herbal therapy is more efficacious and safer than insulin or oral agents. Tablets are oral

insulin. As regards insulin: this drug affects adversely the eyes, the liver and the kidneys. Insulin is addictive (once insulin, always insulin). It should not be taken for fear of hypoglycemia. Insulin leads to pancreatic failure (WHO, 1996)

Hope for Change

The WHO recognizes education as a corner stone in diabetes therapy, which should be tailored to local socio-economic and cultural circumstances. The aim of this work included assessment of: 1) The state of knowledge, practices and attitudes of school children and adolescents with type 1 diabetes and/or their parents. 2) The impact of a short therapeutic education program including projection and discussion of video film. 3) The impact of this program on diabetes control namely HbA1c, frequency of absenteeism, ketoacidosis and hypoglycemic episodes.

A study was conducted on 100 subjects (school children or adolescents) with type 1 diabetes and 56 parents randomly selected from 1600 subjects receiving health care from the Students Diabetes Center in Alexandria. The study comprised 4 phases: 1) Initial pretest assessment, 2) Educational programme including a one-day camp in a sporting club, projection of the video film & interactive discussions, 3) Immediate post-test assessment and 4) Final assessment (3 months later). Data collection comprised: 1) Questionnaire covering knowledge, misconceptions, skills & practices, attitudes & perception. 2) Physical examination. 3) Assay of HbA1c. 4) Review of absenteeism and hospitalization records. The video film describes in 60 minutes the story of a teenager with diabetes who dreams of being visited by a genie. The genie discusses with him basic knowledge about diabetes, local myths, demonstrates skills and practices for management and discusses his attitudes towards the disease and its management.

Less than two per cent of subjects with diabetes or their parents attended any educational activity outside the consultation setting. Eighty two per cent of subjects believed that their disease is temporary. Fifty-six per cent could not recognize or diagnose ketosis. Fifty-two per cent did not know how to adjust insulin dosage. Fifty-two per cent had never changed the site of their injection. Fifty-six per cent never knew about

foot care. Ninety-eight per cent stated that their disease is a barrier against their success.

This study demonstrated the positive impact of this short educational programme. A result peculiarly significant, as the present intervention has been especially designed to the target population; a population with rather poor resources and special cultural background.

Conclusion

Unified protocols for registries should be adopted to be able to compare the evolution of the epidemiology of the disease across time and regions. Registries and surveys should aim at evaluating the prevalence of complications as well as the cost of the disease There is a great need for multicentric controlled, studies to re-evaluate the efficacy of the different intervention strategies on long term basis in a regional context.

References

1. Sicree R., Shaw J., Zimmet P. 2003 'Diabetes and impaired glucose tolerance: Prevalence and projections'. In: Diabetes Atlas, 2nd edition, IDF & WDF. Edit. Delice Can. IDF Brussels, Belgium. Chap. 1 : The global Burden of diabetes; pp 15-71.
2. Herman W.H., Ali M.A., Aubert R.E. Engelgau M.M., Kenny S.J., Gunter E.W., Malarcher A.M., Brechner R.J., Wetterhall S.F., De Stefano F., et al., 1995. 'Diabetes mellitus in Egypt: risk factors and prevalence'. Diabet Med; 12 (12): 1126-31.
3. Arab M. 1992. 'Diabetes in Egypt'. World Health Statistics 45: 334-37
4. Assaad-Khalil et al., 2006. Alexandria University Survey, 1995-2002. A regional population based diabetes registry in Alexandria. Unpublished data.
5. Arab M.M., Abdel Rehim A.1993. 'Socio-economic background for the epidemiology of diabetes mellitus in Mediterranean countries'. Proceedings of the 4th MGSD Meeting. Madrid, 1993. Medicographia 1994; 16 (i) : 84-90
6. Assaad-Khalil S.H. 2005. 'Education & Diabetes in the Arab Region'. Chapter 19: 269-84. In: Diabetes in the Arab World Eds: Abdulfattah Lakhdar & Geoffrey Gill. FSG Communications Ltd Reach, Cambridge, UK; PP 302
7. WHO Document 1996. 'Health Education for People with Diabetes'. (WHO-EM/DIA/7-E/G) WHO, Geneva. Published in 1993 after a Regional Consultation in the EMRO Region
8. Assaad-Khalil S. H., El Siwy F., Kamel K. F., Gaber R. 2003. 'Impact of an educational video film: "The Jinn's Party" on the knowledge, practices and attitudes of school children and adolescents with Type 1 diabetes and their parents.18th IDF Paris 2003; Abstract Number 254.

6

BIOTECHNOLOGY IN AGRICULTURE, FOOD AND THE ENVIRONMENT

30

GM Crops, Food Security and the Environment

Effat Badr

Introduction

Genetic modification, like many other new technologies, has been hailed as one of the keys to economic development, and presented as bringing a wide variety of benefits to people and the environment. But it should be remembered that inherent in the technology itself are impacts on the environment that are far from certain. Assessing the benefits and risks demands a comparison between transgenic and nontransgenic plants. The goal is agricultural sustainability — that is, sustaining levels of production while minimizing environmental impacts.

Environmental and social problems form an interactive, intertwined network. The most pressing socioeconomic problems of our planet are poverty and pollution. Biotechnology provides contributions to how we tackle these problems, not complete solutions. The benefits of appropriately used genetic engineering in agriculture will overweigh any attendant environmental risks. Advances in ecology, population genetics and the social sciences, as well as social dialogue, are needed to make mindful choices on how to create products that are best for both humans and the environment.

The issue of how the environment is being affected by new agricultural technologies is a pressing and often emotive one. The earth is finite in size and in the renewable and non-renewable resources it produces and

contains. Water shortages are already putting several forms of life at risk of extinction. Agriculture is the greatest guzzler in this context, using 70 per cent of the world's water. Meanwhile, the amount of land capable of producing food has fallen to about 0.4 hectares per person.

We are also facing the end of our available fossil fuels. Oil that was formed in prehistoric times at a rate of less than 100 barrels a day is now being consumed at a rate of millions of gallons a day. Moreover, neither oil nor water is distributed fairly among different peoples. The 1990 World Watch Institute report predicts that we have until 2030 to find and implement solutions to these and other grave environmental issues.

One of the biggest challenges is that environmental and social problems form an interactive, intertwined network. The world's population is not simply going to stop growing, even though it is the root cause of all environmental problems. The goal of agricultural plant science is to increase productivity, improve quality and maintain the environment; but this will necessitate producing crop varieties that move us away from chemically dependent agriculture while maintaining or increasing yields, providing novel energy sources (biofuels), sustaining biodiversity and minimizing the environmental impacts of agriculture. Agricultural sustainability is about maintaining levels of production while minimizing the environmental impacts of the technology. In this context, biotechnology provides contributions to solutions, rather than the complete solution.

The vital thing is how we go about putting it all into practice. Environmental literacy and social dialogue are needed if humanity is to divert today's course of self-destruction towards sustainability and peaceful coexistence. Scientists should consider this as part of their obligations to society, and scientists and nonscientists should strive to meet halfway if genetically modified organisms (GMOs) are to be both understood, and sensibly deployed.

GM Food Security and non-GM: Comparing Risks

Attempts to introduce genetically modified (GM) crops, also referred to as biotech crops, have stimulated a negative campaign by those who ignore common farming practice and facts about plants. This group — almost none of whom are plant biologists — has inaccurately presented general problems as being unique to GM plants.

To accurately assess GM crops, it is necessary to compare their performance with that of conventional ones. But the critics had two arguments as to why it is not legitimate to compare the two, centred on the assertion that more serious side effects should be expected with transgenic plants. The first argument is that transgenes insert at random, and may cause mutations in the host genome that can trigger changes in the transformed plant that are unrelated to the information coded in the transgene. The second is that genes can be transferred across species barriers and introduce metabolic pathways alien to the host plant species.

Both arguments refer to hypothetical risks, however. There is no empirical evidence yet that more serious effects do in fact occur in transgenic plants, nor is it possible to anticipate such effects theoretically in any detail. But it is argued that one can infer from the 'specific quality' of genetic engineering that transgenic plants present a 'specific type of uncertainty'.

Going back to those two arguments, the first can be invalidated by pointing out that mutations are not specific to genetic engineering. They also occur with conventional breeding, and when natural transposable elements — which exist in most plants, and also insert at random — jump around in the plant genome.

The second argument, although valid in principle, is also weakened through comparison. It may be true that the probability of side effects is theoretically higher in transgenic plants, if new metabolic pathways are transferred. However, it can also be argued that the probability of side effects is lower in transgenic plants because with genetic engineering, a single identifiable gene product is transferred — whereas with crossing techniques, an uncontrolled number of undetermined genes may be exchanged, all of which can interact with the existing metabolism.

The critics of genetic engineering finally retreated to the argument that even if transgenic plants do not involve more severe risks than nontransgenic plants, it is still theoretically possible that the risks they pose may become apparent later.

It is worth noting in this context that the mutation breeding used today to produce many of the crops we see growing in the countryside involves the use of thermal neutrons, X-rays or ethyl methane sulfonate, a harsh carcinogenic chemical — anything powerful enough to damage DNA. No safety tests have been done on this process, and nobody protests about it.

The irony is that genetic modification was invented in 1983 as a gentler, safer, more rational and more predictable alternative to mutation breeding — an organic technology, in fact. Instead of random mutations, scientists could now add the traits they wanted.

Benefits from GM Crops

GM crops offer a host of benefits to global society. They contribute to global food, feed and fibre, security, protect biodiversity, and promote a safer environment through the conservation of soil, water and pesticides. They provide a range of socioeconomic benefits, including alleviation of poverty and hunger in developing countries.

The year 2005 was the 10th anniversary of the commercialization of GM varieties (1996-2005), when the billionth acre of GM crops was planted. More and more farmers have adopted these crops because they boost yields, keep pesticide use down, enhance biodiversity and are economical. There has not been a single human health problem arising from them. Yet, far from being welcomed as a greener 'green revolution', genetic modification has run into fierce, and well-publicized, opposition from the environmental movement. Because of the protests, the issue of public trust has been a big problem for biotechnology.

The world population now numbers more than six billion, and is projected to be 10 billion by 2050. Feeding that many people will demand at least 35 per cent more calories than the world's farmers grow today, and probably much more if a growing portion of those 10 billion are to have meat more than once a month (it takes 10 calories of weight to produce one calorie of meat). That will mean either better yields or less rainforest, which is why fertilizers, pesticides and transgenes are protectors of the planet.

In her 1962 classic *Silent Spring*, Rachel Carson documents the urgent need to reduce pesticide applications to crops, and asserts that the biodiversity on which we are ultimately dependent must be maintained. The Bt or *Bacillus thurigiensis* insecticidal proteins, which number about 130, selectively kill some beetles and caterpillars and target insects that eat crops. The expression of Bt proteins in cotton and corn has reduced the application of specific highly toxic pesticides by more than 80 per cent,

allowing a return of wildlife to the crop fields. GM crops could also reduce environmental damage resulting from the use of synthetic fertilizers and pesticides and from soil erosion.

Risks to the Environment

Conventional methods of plant improvement produce crops that are not absolutely safe, and we cannot expect GM crops to be absolutely safe either. We should use advanced knowledge in genetics, ecology and the social sciences to make mindful choices about how to create the products that are best for humans and our environment.

Among the potential ecological risks identified are the possibility of transgene flow from GM to non-GM crops and wild relatives in nearby fields. This may allow the spread of traits such as herbicide resistance from genetically modified plants to non-target plants, with the latter potentially developing into an invasive weed. This risk may be assessed when deciding whether a GM crop with a given trait should be released into a particular environment and under what conditions, as well as monitoring its behaviour after release.

Generally, however, herbicide resistance is not as important as resistance to drought, salinity and yield-destroying diseases such as rust or rice blast, or pests such as locusts. In fact, crop-to-weed gene flow has happened in traditional systems of agriculture, and has created hardship through the appearance of new weeds or ones that are harder to control. Such spontaneous hybridization with wild relatives has been implicated in the evolution of more aggressive weeds for seven of the world's most important crops. Moreover, crop-to-weed gene flow can send a rare species to extinction—as happened with a wild subspecies of rice.

Other potential ecological risks have stemmed from the widespread use of corn and cotton genetically modified to carry Bt genes, which may lead to the development of resistance to Bt in insect populations exposed to the crops. One way of managing this risk is to plant 'refuge' sections of Bt cotton fields with insect-susceptible varieties to reduce chances for the insect population to evolve towards Bt resistance. Bt plants may also carry a risk for non-target species such as birds and butterflies. The monitoring of these effects on the environment and the devising of effective risk management approaches is essential.

Crops can be engineered to directly clean up environmental problems. For instance, GM plants can be used for bioremediation, selectively absorbing various metal complexes such as aluminum, copper, mercury and cadmium from contaminated soils. One such use could be removing methyl mercury in soils, which will also take it out of the food chain.

Researchers have also genetically modified aspen trees to produce 50 per cent less lignin and 15 per cent more cellulose. Thus, 15 per cent more pulp may be produced from the same amount of wood. Moreover, the GM trees are 25 to 30 per cent taller. So the land, chemicals and energy used to make a given quantity of paper can be reduced substantially and result in significantly lower environmental impacts at every stage, from tree farming to paper production.

Other potential applications that could reduce environmental impacts include the production of biodegradable plastics and of coloured cotton, which could reduce reliance on synthetic dyes.

Conclusion

What does the future of using biotechnology to improve crops look like? A key element is the evaluation of risk to human health and the environment. Agriculture will also need to be technologically both flexible and diverse, and use land efficiently. Integrated pest management systems will need to be developed. Water will become an increasingly expensive commodity and a premium will be set on crops that use water efficiently without loss of yield.

Ultimately, our ability to assess the contribution of agricultural biotechnology will depend on our ability to identify and measure its potential benefits and risks. Governments and scientists should effectively communicate with the public about the nature of new crop types and varieties, and about the risks and benefits of agricultural biotechnology in their own country and internationally. The pressing environmental problems are not technical ones, but demand changes in personal beliefs and aspirations. As the population genetics pioneer J.B.S. Haldane said in 1939, "Changes are induced by struggle as much as by argument and it is necessary to recognize this fact, even when you are doing your best to introduce some reason into the process."

References

1. Ellstrand, N., Prentice, H. and Hancock, J. 1999. Gene flow and introgression from domesticated plants to their wild relatives. Annual Review of Ecological Systems. No. 30, pp 539-563
2. Fernandez-Cornejo, J. and Caswell, M. 2006. The 1st decade of genetically engineered crops in the United States. USDA Economic Information Bulletin. No.11, pp 1-36. Available at: http://www.ers.usda.gov
3. Fitt, G., Llewellyn, D. and Mares, C. 1994. Field evaluation and potential impact of cotton (*Gossypium hirsitum*) in Australia. Biocontrol Science and Technology. Vol.4, No.4, pp 535-548. Available at: www.econ.ag.gov/whatsnew/issues.biotech
4. Lusk, J., Jamal, M., Kurlander, L. et al. 2005. A meta analysis of genetically modified food evaluation studies. Journal of Agricultural and Resource Economics. No. 30, pp 28-44
5. Persley, G. and Siewdow, J. 2002. Applications of biotechnology to crops: benefits and risks. In Ruse, M. and Castle, D. (eds). Genetically modified foods. Prometheus Books, New York, USA. pp 221-233
6. Solh, M., P. Kenmore and J. Hyman. 2005. Agrobiodiversity, people and the environment. In Serageldin, I. and Persley G. (eds). Discovery to delivery: Biovision Alexandria 2004. Bibliotheca Alexandrina, Alexandria, Egypt. Pp 159-173
7. Tilman, D. 1998. The greening of the green revolution. Nature. Vol. 396, No. 6708, pp 211-212
8. Wallace, B. 1998. The environment as I see it, science is not enough. Elkhorn Press, Elkhorn, West Virginia, USA, pp 3-35

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Potential Environmental Impacts from Novel Crops

Brian Johnson

Introduction

Water, especially water for irrigated agriculture, is fast becoming one of the most precious commodities on Earth. This is partly because modern agriculture demands constant soil moisture for optimum yields, but also because agriculture is competing for water with the growing conurbations and patterns of increasing personal consumption that characterise modern development in both developed and developing countries.

Agriculture increasingly relies on irrigation, with around 10 per cent irrigated cropland worldwide in 1960 rising to 20 per cent today, with this irrigated land contributing to about 40 per cent of the worlds food production (WRI, 2000; FAO, 2004). In Asia the area of irrigated land has risen from 8 per cent in 1960 to over 10 per cent today, mostly for rice cultivation (WRI). Irrigation for agriculture now accounts for around two thirds of all abstraction and three quarters of water consumed. Urban use accounts for only a tenth of abstraction, and industry uses about one fifth, but demand in both these sectors is growing rapidly especially in Asia and Latin America (IPCC, 2001), leaving less for agriculture. Increasing demand for irrigation water is a cause of conflict in some parts of the world and, where water supplies are limited, tends to work against the interests of poor farmers favouring those who can afford the infrastructure, labour and other costs associated with irrigation. Agricultural irrigation areas

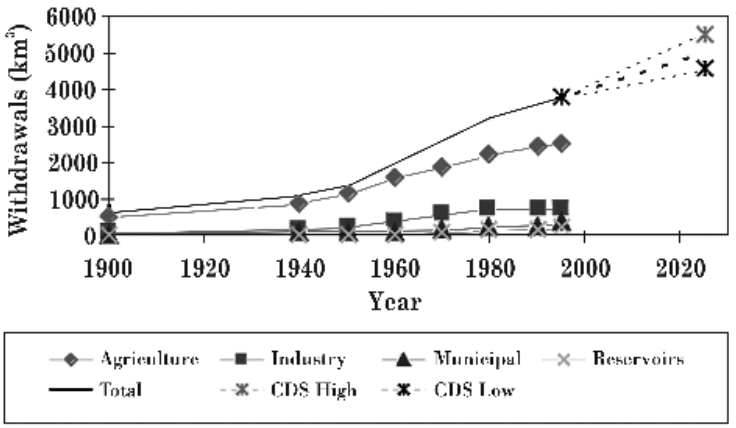

Figure 1. Global water withdrawals, 1900–1995, with projected future total withdrawals to 2025 [chart from IPCC 2001]. CDS is the IPCC Conventional Development Scenario used in climate change modelling.

can also be unsustainable, with abstracted groundwater volumes greatly exceeding replenishment rates (FAO, 2004), resulting in lowered water tables in many arid areas.

Not only has the demand for crop irrigation been increasing, but so also have droughts, both in frequency and intensity, probably as a result of increased global warming (IPCC, 2001). Huge areas of previously cultivated land are now relatively unproductive due to recurrent droughts and year-on-year decreases in annual rainfall. This can be illustrated by the situation in the Indus Valley in Pakistan, where severe droughts were relatively rare 50 years ago but are now so common that many farmers have abandoned land because the droughts and high temperatures have led to salinization of seasonally waterlogged soils (UNEP, 2000). This happens when surface evaporation of irrigation and floodwaters deposit more and more salts (sodium and potassium chlorides (salinity) and sulphates (sodicity)) with each year of cultivation (FAO, 2003a). Drought and salinization are now adversely affecting agricultural production over much of the tropical part of the globe, producing so-called 'solonchak' soils in the Middle East, Central Asia, South America and parts of Africa and Australia (FAO, 1998).

Given current trends in consumption and energy use, climate change is unlikely to be mitigated this century (IPCC, 2001), but there may be ways that crop scientists can adapt many crops to increasingly dry and salty soils, and at the same time produce arable management systems that require far less irrigation water than on normal soils. Such crops would give an opportunity to obtain better yields from marginal arid areas, and if used on as yet unsalinized soils, could delay the onset of salinization, reducing the risk of farmers inadvertently ruining their land.

Tolerance to Drought and Salinity in Nature

In some cases it is possible to find genetically-determined salt, sodic and drought tolerance within crop gene pools and the gene pools of crop ancestors. If the genes are present and can be activated, then they can be moved into the crop of interest by conventional plant breeding. Plant breeders have been searching for such genes for many decades and in some cases have been successful, producing crops that can be used by small farmers in arid areas where drought and salt-tolerant crops can save the livelihoods of whole communities. Examples of this approach are the salt and sodic tolerant rice and wheat produced by CSSRI India, using traits they have found to occur naturally in the modern crops' ancestors, and breeding these into high yielding dwarf varieties that are the backbone of rice and wheat production in Asia. Their CSR10 rice can grow well in pH 10.5 sodic soils, and KRL19 wheat survives salinities that kill conventional wheat crops (CSSRI, 2001). Other examples from conventional breeding include maize variety ZM521, which yields up to 50 per cent more than traditional varieties under drought conditions (CIMMYT, 2003).

But conventional plant breeding techniques are a very slow way of introducing salt and drought-tolerance into crops, and of course rely on the tolerance genes being present in species and varieties that are either sexually compatible with the crops, or can be introduced using techniques such as embryo rescue or cell fusion.

In the past decade, genes that confer general tolerance to drought and salinity have been found in many organisms, including the model plant *Arabidopsis thaliana*, other plants not related to crops such as wild xerophytic plants (including 'resurrection' plants), and in microorganisms

such as bacteria. The challenge for plant breeders has been to transfer these genes into crops and to get them to express the traits.

Salt and Drought Tolerance Genes From Species Other Than Crops

Biotechnology is by far the most rapid and effective way to transfer genes from unrelated species into crops. The discovery of the *Dreb* series of genes in *Arabidopsis* prompted great interest in the 1990s because it was realised that these genes conferred general drought and salt tolerance that could be readily expressed in crops. In a short time crop breeders such as those at CIMMYT had transferred the *Dreb1A* gene into crops such as wheat, producing varieties that could withstand prolonged drought, and could be grown using far less irrigation water than conventional cultivation (CIMMYT, 2004). AGERI, based in Cairo, are developing a transgenic wheat with the *HVAI1* gene from barley that shows great promise in arid conditions (New Agriculturalist, 2004, AGERI, 2005). Researchers at Cornell University have recently discovered that trehalose sugar genes from *E. coli* give salt and drought resistance in rice (Su et al., 1998, Garg et al., 2002). These developments are scientifically exciting and show great promise agriculturally, but are they safe to use in the environment and will their use truly give more sustainable cropping systems in arid conditions?

Potential Environmental Impacts from Salt and Drought Tolerant Novel Crops

There are potential environmental impacts arising from these new crops no matter how salt and drought tolerance is introduced; whether by conventional or by transgenic methods. Over the past 20 years regulators have developed systems for assessing risks from transgenic crops, but (with the exception of Canadian regulators) have virtually ignored potential risks from crops produced by other methods. Risks from novel crops may be classified as either 'direct' risks arising from characteristics of the crop itself or 'indirect' risks arising from the management systems used

to grow the crop (Johnson, 2004). For crops with traits such as salt and drought tolerance direct impacts might include possible invasiveness and gene flow to wild relatives and ancestors, whilst indirect risks might stem from changes in crop management, range and extent.

Possible invasiveness

Saline and arid soils support relatively simple ecosystems with much bare soil in habitats such as estuaries, littoral zones and deserts. Such areas are known to be vulnerable to invasion by non-native species and hybrids (Phillips and Comus, 2000, Wasson et al., 2002, EPA, 2006). In European estuaries we have the classic case of invasion by Spartina anglica, a hybrid grass that seems to have arisen spontaneously from two introduced species (Hubbard, 1965), demonstrating that gene flow between closely related species can produce a hybrid that is fitter than the parents in certain habitats (Hubbard & Stebbings, 1967). Invasion of arid and salty environments by non-native species is very common illustrated by the prickly pear Opuntia in Australia (Humphries et al., 1991), and Tamarisk and several alien grasses in arid zones of the southwestern United States (Brooks and Pyke, 2001). So there is clearly potential for salt and drought tolerant plants to invade dry salty soils, but is this likely for crops? Fortunately most arable crops are annuals and most have been so heavily adapted to the artificiality of agriculture that they are unable to survive and reproduce in the wild; they can be described as ecologically disabled. Because many crops carry such high 'genetic loads', even the addition of salt and drought tolerance may not increase their fitness sufficiently to allow them to invade natural habitats. However there may be more serious future issues with salt and drought tolerance in perennials such as trees and ornamentals, where artificial selection has not moved genomes very far from wild-type and where their longevity and copious seed and pollen production pose special risks.

Although researchers and regulators may see risks of invasiveness from salt and drought tolerant plants as low, these traits are potentially fitness-enhancing and there is therefore a need for close scrutiny before they are released into the wider environment. Perhaps the only scientifically defensible risk assessment for these plants would be to deliberately introduce salt and drought tolerant crop plants into natural habitats (with

strict experimental controls) and monitor their performance in a similar way to the experiments carried out in Britain in the 1990s (Crawley et al., 2001).

Gene flow

There is a high probability that salt and drought tolerant genes introduced into crops will end up in wild relatives and ancestral plants – even from conventionally bred crops. Rates of gene flow between crops and their relatives and ancestors have been measured for many years (for example Scheffler et al., 1993, Ellstrand et al., 1999) and, although gene transfer very often occurs, rates are usually low. The most obvious candidate recipients for such gene transfer would be 'weedy' rice species, legumes and cereal ancestors, all of which can be sexually compatible with the equivalent crops. There is a small but real possibility that salt and drought tolerance genes could increase fitness and invasiveness of recipient wild plants, some of which (such as weedy rice) are already either invasive of marginal agricultural land or are weeds within crops. Although much is known about the mechanisms and rates of gene transfer between crops and wild relatives, relatively little research has been conducted on the impacts of crop genes transferred to wild plants (Johnson, 2004). Perhaps the best way to assess the risk of enhanced fitness is by putting salt and drought tolerance genes into wild plants that are candidate recipients, and measuring components of fitness in the wild. This is potentially risky and would be strictly controlled by regulators but, as (Snow et al., 2003) have shown, such experiments can be done safely by using gene restriction techniques such as male sterility to prevent pollen flow.

Potential Indirect Impacts

Changes in management systems

Although there has been extensive research on the development of salt and drought tolerant crops, there appears to have been little effort made to develop management systems by which these crops would be grown. This aspect of arable farming tends to be left to farmers and agronomists to decide, and there is some merit in this. However, regulators are increasingly

concerned about the relative sustainability of different cropping systems, compared to those used now in 'conventional' agriculture. The question of *how* these crops will be grown is of great interest not only to regulators but also to those responsible for land management strategies, including agriculture ministries and water authorities. Specifically they would like to able to compare the impacts of novel cropping systems on soil and water quality and water usage, on nutrient balances, and on non-crop biodiversity. There are also issues about the contributions of cropping systems to climate change and whether novel systems will achieve a better overall carbon balance.

There is also increasing concern about *where* such novel crops would be grown. Salt and drought tolerant crops could be grown on the vast areas of semi-desert and abandoned farmland in arid areas, and salt tolerant rice could be grown in coastal saline habitats that are an increasing feature in low-lying areas subject to sea level rise. Introducing such crops to these habitats could have major impacts on soils and on biodiversity.

There are also considerable potential benefits in using salt and drought tolerant crops. Early experiments (reported in FAO, 2003b) indicate that some crops, especially rice and wheat, could use up to 70 per cent less water to achieve equivalent yields. This would be a highly desirable outcome of their use, reducing salinization, irrigating more land area at lower costs, and potentially producing better nutrient usage with less leaching and surface run-off. All this points towards more sustainable production systems than at present. There is also the possibility of using salt and drought tolerant plants specifically to conserve rainfall and reduce soil erosion in arid areas, and the intriguing possibility of using these plants to desalinate already contaminated land.

Conclusion

Given the current interest in sustainability from regulators and governments worldwide, the question arises of whether sufficient attention has been given to impact assessment of drought and salt tolerant crops. Saline and arid environments are ecologically vulnerable habitats with potential invasion issues and more research needs to done not only on the ecological characteristics of the crops themselves but also on rates and especially the impacts of gene flow from salt and drought tolerant crops to wild plants.

The potential benefits need to be quantified by using field trials that compare the new cropping system with conventional systems, especially for measuring water conservation, energy inputs and salinization impacts. These experiments need not be costly and complex, but sufficient to quantify characteristics of salt and drought tolerant cropping systems that are currently the subject of regulatory and political scrutiny.

The promise of better cropping systems may not be fulfilled unless these issues are addressed by both science and policy. Action is needed urgently because water for agriculture in arid regions is fast becoming a scarce and valuable resource, limiting the capacity of poor people to feed themselves.

References

1. AGERI 2005 Breeding Triticum durum in Mediterranean Region by Using in vitro & Genetic Transformation Tools. Available at http://www.ageri.sci.eg/topic6/durum.htm
2. Brooks, M. L. and D. A. Pyke. 2001. Invasive plants and fire in the deserts of North America. Pages 1–14 in K. E. M. Galley and T. P. Wilson (eds.), Proceedings of the Invasive Species Workshop: The Role of Fire in the Spread and Control of Invasive Species. Fire Conference 2000: The First National Congress on Fire Ecology, Prevention, and Management. Miscellaneous Publication No. 11. Tall Timbers Research Station, Tallahassee, FL.
3. Crawley, M.J., Brown, SL, Hails, RS, Kohn DD, Rees M., 2001,Transgenic crops in natural habitats, Nature, Vol: 409, Pages: 682 - 683
4. CSSRI 2001 Development and Adoption of Salt Tolerant Crop Varieties at Central Soil Salinity Research Institute (Karnal, India) available at: http://www.plantstress.com/Files/Salt_Karnal.htm
5. CIMMYT 2003 Drought Relief, Seed Relief in Sight available at http://www.cimmyt.cgiar.org/whatiscimmyt/recent_ar/D_Support/drought.htm
6. CIMMYT 2004 Molecular Approaches for the Genetic Improvement of Cereals for Stable Production in Water Limited Environments. J-M Ribaud and D Poland Editors. Available at: http://www.cimmyt.org/english/docs/proceedings/molecApproaches/pdfs/MolecularApproaches.pdf
7. Ellstrand N.C., Prentice H.C., Hancock J.F. (1999) Gene flow and introgression from domesticated plants into their wild relatives. Ann Rev Ecol Syst 30: 539-563
8. FAO 1998 Global Map of Solonchak Soils available at: http://www.fao.org/WAICENT/FAOINFO/SUSTDEV/EIdirect/gis/EIgis000.htm

9. FAO 2003a Groundwater Management - The Search for Practical Approaches available at: http://www.fao.org/DOCREP/005/Y4502E/Y4502E00.HTM
10. FAO 2003b Report of the FAO Expert Consultation on Environmental Effects of Genetically Modified Crops, 16 - 18 June 2003, FAO Rome, Italy
11. FAO 2004 Water Resources Development and Management Services Division available at: http://www.fao.org/ag/agl/aglw/
12. Garg, A.K., Kim, J.-K., Owens, T.G., Ranwala, A.P., Choi, Y.D., Kochian, L.V. and Wu, R.J., 2002, Trehalose accumulation in rice plants confers high tolerance levels to different abiotic stresses. Proc. Nat. Acad. Sci. USA 99, 15898-15903.
13. Hubbard, J.C.E. 1965, Spartina Salt Marshes in Southern England. VI. Pattern of Invasion in Poole Harbour, Journal of Ecology, 52, 79-94.
14. Hubbard, J.C.E., & Stebbings, R.E. 1967. Distribution, date of origin and acreage of Spartina townsendii (s.l.) marshes in Great Britain. Proceedings of the Botanical Society of the British Isles, 7: 1-7.
15. Humphries, S.E., R.H. Groves, and D.S. Mitchell. 1991. Plant invasions and Australian ecosystems: a status review and management directions. In: Plant Invasions: The incidence of Environmental Weeds in Australia. Australian National Parks and Wildlife Service, Canberra, Australia, pp. 1-127.
16. IPCC 2001, Climate Change 2001: Working Group II: Impacts, Adaptation and Vulnerability, Chapter 4: Hydrology and Water Resources. Intergovernmental Panel on Climate Change, Geneva. Available at: http://grida.se/climate/ipcc_tar/wg2/159.htm
17. Johnson, B. R., 2004 Gene flow from crops to crops and from crops to wild relatives – does it matter ecologically? Pp. 53-65 Aspects of Applied Biology 74, GM crops – Ecological Dimensions Eds. H.F. van Emden & A.J.Gray, AAB, Wellesbourne, UK
18. New Agriculturalist on Line 2004, GM Wheat for the Desert, available at: http://www.new-agri.co.uk/04-6/newsbr.html#nb10
19. Phillips, S. J. and Comus, P.W. 2000, A Natural History of the Sonoran Desert. Arizona-Sonora Desert Museum Press: Tucson.
20. Scheffler, J.A., Parkinson R. and Dale P.J., 1993, Frequency and Distance of Pollen Dispersal from Transgenic Oilseed Rape (Brassica napus), Transgenic Research 2, p. 356-364.
21. Shiklomanov, I.A., 1998, Asssessment of water resources and water availability in the world. Background Report for the Comprehensive Assessment of the Freshwater Resources of the World. Stockholm Environment Institute, Stockholm, Sweden, 88 pp.
22. Shiklomanov, I.A. and V.Yu. Georgiyevsky, 2001, Anthropogenic global climate change and water resources. In: World Water Resources at the Beginning of the 21st Century. UNESCO, Paris, France, (in press).
23. Snow, A. A., D. Pilson, L. H., Paulsen M., Pleskac N., Reagon M. R., Wolf D. E., and Selbo S. M., 2003. A Bt transgene reduces herbivory and enhances fecundity in wild sunflowers. Ecological Applications 13:279-286.
24. Su, J., Shen, Q., Ho, T.-H.D. and Wu, R., 1998, Dehydration-stress-regulated transgene expression in stably transformed rice plants. Plant Physiol. 117, 913-922.

25. UNEP 2000 Protecting rural groundwater quality: in Groundwater and its susceptibility to degradation available at: http://www.unep.org/DEWA/water/groundwater/pdfs/Groundwater_85-104_SCREEN.pdf
26. Wasson K., Lohrer D., Crawford M., Rumri S., 2002, Non-Native Species In Our Nation's Estuaries; A Framework For An Invasion Monitoring ProgramNERRS Technical Report Series: 1, available at: http://www.nerrs.noaa.gov/Invasive/Report.html
27. WRI (World Resources Institute) 2000, Will there be enough water? Available at http://earthtrends.wri.org/features/view_feature.php?theme=2&fid=17

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A Decade of Agricultural Biotechnology

Clive James

Introduction

The year 2005 marked the tenth anniversary of the commercialization of genetically modified (GM) or transgenic crops, now more often called biotech crops. In 2005, the billionth acre, equivalent to the 400 millionth hectare of a biotech crop, was planted by one of 8.5 million farmers, in one of 21 countries. This unprecedented high adoption rate reflects the trust and confidence of millions of farmers in crop biotechnology. Over the last decade, farmers have consistently increased their plantings of biotech crops by double-digit growth rates every single year since biotech crops were first commercialized in 1996, with the number of biotech countries increasing from 6 to 21 in the same period. Remarkably, the global biotech crop area increased more than fifty-fold in the first decade of commercialization.

GM Crops Around the World

The global area of approved biotech crops in 2005 was 90 million hectares, equivalent to 222 million acres, up from 81 million hectares or 200 million acres in 2004. The increase was 9.0 million hectares or 22 million acres, equivalent to an annual growth rate of 11 per cent in 2005. An historic

milestone was reached in 2005 when 21 countries grew biotech crops, up significantly from 17 countries in 2004. Notably, of the four new countries that grew biotech crops in 2005, compared with 2004, three were EU countries, Portugal, France, and the Czech Republic whilst the fourth was Iran.

Portugal and France resumed the planting of Bt maize in 2005 after a gap of five and four years respectively, whilst the Czech Republic planted Bt maize for the first time in 2005, bringing the total number of EU countries now commercializing modest areas of Bt maize to five, viz: Spain, Germany, Portugal, France and the Czech Republic.

Bt rice, officially released in Iran in 2004, was grown on approximately 4000 hectares in 2005 by several hundred farmers who initiated commercialization of biotech rice in Iran and produced supplies of seed for full commercialization in 2006. Iran and China are the most advanced countries in the commercialization of biotech rice, which is the most important food crop in the world, grown by 250 million farmers, and the principal food of the world's 1.3 billion poorest people, mostly subsistence farmers. Thus, the commercialization of biotech rice has enormous implications for the alleviation of poverty, hunger, and malnutrition, not only for the rice growing and consuming countries in Asia, but for all biotech crops and their acceptance on a global basis. China has already field-tested biotech rice in pre-production trials and is expected to approve biotech rice in the near-term.

In 2005, the US, followed by Argentina, Brazil, Canada and China continued to be the principal adopters of biotech crops globally, with 49.8 million hectares planted in the US (55 per cent of global biotech area) of which approximately 20 per cent were stacked products containing two or three genes, with the first triple gene product making its debut in maize in the US in 2005. The stacked products, currently deployed in the US, Canada, Australia, Mexico, and South Africa and approved in the Philippines, are an important and growing future trend which is more appropriate to quantify as 'trait hectares' rather than hectares of adopted biotech crops. Number of 'trait hectares' in the US in 2005 was 59.4 million hectares compared with 49.8 million hectares of biotech crops, a 19 per cent variance, and globally 100.1 million 'trait hectares' versus 90 million hectares, a 10 per cent variance.

The largest increase in any country in 2005 was in Brazil, provisionally estimated at 4.4 million hectares (9.4 million hectares in 2005 compared with 5 million in 2004), followed by the US (2.2 million hectares), Argentina (0.9 million hectares) and India (0.8 million hectares). India had by far the largest year-on-year proportional increase, with almost a three-fold increase from 500,000 hectares in 2004 to 1.3 million hectares in 2005.

Biotech soybean continued to be the principal biotech crop in 2005, occupying 54.4 million hectares (60 per cent of global biotech area), followed by maize (21.2 million hectares at 24 per cent), cotton (9.8 million hectares at 11 per cent) and canola (4.6 million hectares at 5 per cent of global biotech crop area).

Herbicide Tolerence, Inset Resistance

During the first decade, 1996 to 2005, herbicide tolerance has consistently been the dominant trait followed by insect resistance and stacked genes for the two traits. In 2005, herbicide tolerance, deployed in soybean, maize, canola and cotton occupied 71 per cent or 63.7 million hectares of the global biotech 90.0 million hectares, with 16.2 million hectares (18 per cent) planted to Bt crops and 10.1 million hectares (11 per cent) to the stacked genes. The latter was the fastest growing trait group between 2004 and 2005 at 49 per cent growth, compared with 9 per cent for herbicide tolerance and 4 per cent for insect resistance.

Biotech crops were grown by approximately 8.5 million farmers in 21 countries in 2005, up from 8.25 million farmers in 17 countries in 2004. Notably, 90 per cent of the beneficiary farmers were resource-poor farmers from developing countries, whose increased incomes from biotech crops contributed to the alleviation of their poverty. In 2005, approximately 7.7 million poor subsistence farmers (up from 7.5 million in 2004) benefited from biotech crops – the majority in China with 6.4 million, 1 million in India, thousands in South Africa including mainly women Bt cotton farmers, more than 50,000 in the Philippines, with the balance in the seven developing countries which grew biotech crops in 2005. This initial modest contribution of biotech crops to the Millennium Development Goal of reducing poverty by 50 per cent by 2015 is an important development which has enormous potential in the second decade of commercialization from 2006 to 2015.

In 2005, the 21 countries growing biotech crops included 11 developing countries and 10 industrial countries; they were, in order of hectarage, USA, Argentina, Brazil, Canada, China, Paraguay, India, South Africa, Uruguay, Australia, Mexico, Romania, the Philippines, Spain, Colombia, Iran, Honduras, Portugal, Germany, France and the Czech Republic. During the period 1996 to 2005, the proportion of the global area of biotech crops grown by developing countries has increased every year. More than one-third (38 per cent, up from 34 per cent in 2004) of the global biotech crop area in 2005, equivalent to 33.9 million hectares, was grown in developing countries where growth between 2004 and 2005 was substantially higher (6.3 million hectares or 23 per cent growth) than industrial countries (2.7 million hectares or five per cent growth). The increasing collective impact of the five principal developing countries (China, India, Argentina, Brazil and South Africa) representing all three continents of the South, Asia, Latin America and Africa, is an important continuing trend with implications for the future adoption and acceptance of biotech crops worldwide.

In the first decade, the accumulated global biotech crop area was 475 million hectares or 1.17 billion acres, equivalent to almost half of the total land area of the US or China, or 20-times the total land area of the UK. The continuing rapid adoption of biotech crops reflects the substantial and consistent improvements in productivity, the environment, economics, and social benefits realized by both large and small farmers, consumers and society in both industrial and developing countries.

The most recent survey of the global impact of biotech crops for the nine-year period 1996 to 2004, estimates that the global net economic benefits to crop biotech farmers in 2004 was $6.5 billion, and $27 billion ($15 billion for developing countries and $12 billion for industrial countries) for the accumulated benefits during the period 1996 to 2004; these estimates include the benefits associated with the double cropping of biotech soybean in Argentina. The accumulative reduction in pesticides for the period 1996 to 2004 was estimated at 172,500 MT of active ingredient, which is equivalent to a 14 per cent reduction in the associated environmental impact of pesticide use on these crops, as measured by the Environmental Impact Quotient (EIQ) – a composite measure based on the various factors contributing to the net environmental impact of an individual active ingredient.

In the first decade of commercialization biotech crops have had significant positive impact on: enhanced crop productivity and farmer income in both industrial and developing countries; protection of biodiversity; sustainability and the environment, through decreased use of pesticides, control of soil erosion and conservation of moisture by enhancing low and no-till practices; stabilizing yields through better control of biotic stresses; and contributed to the alleviation of poverty by increasing the income of small resource poor framers in developing countries who have been major beneficiaries of biotech crops.

Conclusion

There is cause for cautious optimism that the stellar growth in biotech crops, witnessed in the first decade of commercialization, 1996 to 2005, will continue and probably be surpassed in the second decade 2006-2015. The number of countries adopting the four current major biotech crops is expected to grow up to factor of two. Similarly, global hectarage of biotech crops and the number of farmers planting them are also expected to increase by up to a factor of two, as the first generation of biotech crops is more widely adopted and the second generation of new applications for both input and output traits becomes available. Beyond the traditional agricultural products of food, feed and fiber, entirely novel products to agriculture will emerge including the production of pharmaceutical products, oral vaccines, specialty and fine chemicals. Importantly, the use of renewable crop resources to produce ethanol and bio-diesel to substitute non-renewable, polluting, and increasingly expensive fossil fuels, is expected to surge significantly. In the near term, in the established industrial country markets growth in stacked traits, measured in 'trait hectares' of biotech crops, will continue to grow with the introduction of new input and output traits stacked to create value and to meet the multiple needs of both consumers and producers who seek more nutritional and healthier food and feed at the most affordable prices. Adherence to good farming practices with biotech crops will remain critical as it has been during the first decade and continued responsible stewardship must be practiced, particularly by the countries of the South, which will be the major deployers of biotech crops in the coming decade.

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Protecting Livestock Through Genomics

Vishvanath Nene

Introduction

There is an urgent need to improve food security and agricultural productivity, particularly in developing countries. More than 800 million people do not eat enough to meet their daily energy needs. The poor are getting poorer and their problems are exacerbated by diseases such as AIDS, malaria and TB as well as civil unrest and armed conflict. Estimates suggest at least one third of the disease burden in developing countries is due to malnutrition. A number of the challenges that face us in redressing this imbalance require political, policy, economic or social reform but many biotic problems such as disease can be tackled by application of modern biotechnologies.

It is pertinent to understand the importance of livestock to people in developing countries. Besides the obvious value of livestock as foods, meat and milk contain essential micronutrients that are required for health. Livestock provide power, manure for nutrient recycling and a means of transportation. The sale of livestock products can provide a daily income, livestock are prized possessions and often represent a form of asset building and social security. Finally, the livestock industry forms a substantial portion of the agricultural GDP of many developing countries.

The smallholder dairy farm sector in eastern, central and southern Africa is an important one not only in terms of the food products it generates but this sector also offers a means of poverty reduction. Typically such farmers keep one or two cattle and livestock diseases are common. For example, East Coast fever (ECF) poses a severe threat to the livelihoods of these farmers. Losses due to this disease amount to more than $168 million a year (Mukebhi et al., 1992). The disease is caused by a parasite called *Theileria parva* which is transmitted by ticks (Norval et al., 1992). The parasite invades and lives within cattle white blood cells and causes them to behave like cancer cells. ECF is usually an acute disease causing death in an infected animal 3-4 weeks post infection. About 25 million cattle are at risk and it is estimated that there are a million deaths per year. These are economic burdens that the region cannot afford.

One of the research mandates of the International Livestock Research Institute (ILRI), which is headquartered in Nairobi, Kenya, is to develop improved methods of East Coast fever control. ILRI has spent a considerable portion of its research manpower in studying the parasite as well as understanding mechanisms that mediate immunity to infection. In particular, immune responses generated by a live infection and treatment of immunization (Radley et al., 1981) have been studied in great detail with the aim of developing a subunit vaccine for the control of ECF. ILRI made a strategic decision to acquire the genome sequence of *T. parva* to underpin its research activities on the pathogen as well as its vaccine development program. This paper outlines the collaborations that were required to achieve this goal, the science that was developed and the lessons learnt.

The Genomics Revolution and Disease-Related Research

The ability to acquire the complete DNA sequence of an organism has resulted in a paradigm shift in the biological sciences. A genome sequence represents the genetic blueprint of an organism, a code that can be interpreted in the context of its biology using bioinformatics and used to create an electronic knowledge base for that organism. From DNA sequence data a reasonable attempt can be made to predict the genes that are present in it and its molecular composition. The identification of genes,

assignment of function to predicted gene products and reconstruction of organism biology is still in its infancy, and much remains to be described even for model organisms. But genomics provides a powerful framework from which systematic and comprehensive studies can be launched to study and solve problems in biology.

The genome sequence of pathogens provides unprecedented opportunities to understand pathogen biology and to develop improved methods for the control of diseases. DNA sequence data may be used to develop sophisticated genome wide diagnostic markers for pathogen identification as well as population studies (Sullivan et al., 2005), new drug targets may be revealed by inferring the metabolic potential of pathogens (Tripathi et al., 2005) and novel vaccine antigens may be identified by a process of reverse vaccinology (Wack and Rappuoli, 2005). The increasing availability of genome sequence data from diverse organisms (Liolios et al., 2006) is giving way to a systems approach where pathogen biology is now studied in the context of other organisms in its environment, either as free living entities or in symbiotic association with a mammalian or invertebrate host.

Reverse Vaccinology in Subunit Vaccine Development

For *T. parva* and other pathogens the genome sequence in theory provides a list of all parasite protein antigens including those that may play a role in mediating immunity to infection. Two questions arise. Is it possible to identify relevant antigens for vaccine development from the whole list of parasite proteins derived from a genome sequence, and second will vaccination with the identified antigens induce immunity to infection?

The route of reverse vaccinology is to use bioinformatics tools to select antigens that might be targets of the immune response, usually those that are secreted or present on the surface of the pathogen, and to then empirically determine whether vaccination with a selected list of candidate antigens induces immune responses that will kill the pathogen or prime immunity to disease. This approach is independent of immune responses generated during the course of infection and thus reveals antigens via a 'reverse' approach. Various levels of sophistication can be layered over this approach to narrow the list of antigens for *in vivo* studies. For example,

comparative genomics may be used to further prioritize a list of candidate vaccine antigens and immuno-screens of selected antigens may be carried out using immune reagents that are known to correlate with immunity.

Immunity to ECF appears to be dependent on the generation of MHC class I restricted cytotoxic T lymphoctyes (CTLs) that recognize and kill bovine cells that are infected with an intracellular form of the parasite called the schizont (Morrison et al., 1995). Antigen-specific CTL lines and clones can be established *in vitro* and these may be used as immuno-screening reagents. The immunobiology of CTL target cell recognition predicts that a list of secreted *T. parva* proteins will contain candidate vaccine antigens, a group of proteins that can be identified by the presence of a secretion signal motif at the N-terminus. Transfection of these genes into appropriate antigen-presenting cells followed by immuno-screening with the CTLs should, therefore, reveal the antigens that are targeted by protective immune responses.

Setting the Scene for Development of a Prototype Vaccine Against ECF

ILRI was able to partner with The Institute for Genomic Research (TIGR), a private not-for-profit research institute in the USA, to sequence the genome of *T. parva* leading to publication of this work in 2005 (Gardner et al., 2005). Prior to the genome project about 30 parasite genes had been characterized. We now know that the parasite encodes as many as 4068 proteins. Approximately 400 proteins fall into the category of secreted proteins and scientists at ILRI have cloned about 25 per cent of the genes in this list. In case the 'cherry picking' approach missed identification of important vaccine related genes, a random immuno-screen of a library of ~ 60,000 cDNAs representing genes expressed in the schizont stage of the parasite was also undertaken. This technology was developed by ILRI in collaboration with scientists at the Ludwig Institute for Cancer Research in Brussels. Screens of both gene sets have so far led to the identification of five antigens (Graham et al., 2006).

The immune response in cattle to the candidate vaccine antigens have been assessed by ILRI using vaccination technologies developed by

scientists from the University of Oxford and Merial, a veterinary vaccine company, and in collaboration with them. Nineteen of 24 cattle mounted an IFN-γ response and on challenge with a lethal dose of parasites 7 of these cattle which also mounted a cytolytic response were immune to severe disease; all animals in a non-vaccinated group were susceptible to disease (Graham et al., 2006). This is exciting data as it provides proof-of-concept of the approach that was adopted and the assays that were developed. Current efforts are focused on improving the priming of cytolytic responses. However, given the success achieved to date it is ironic that the next research phase, improving the efficacy of the prototype ECF vaccine is under funded.

Lessons From a Remarkable Success Story

Adoption of non-conventional approaches to vaccine development has resulted in many breakthroughs for ECF related research and several important lessons were learnt in achieving the research milestones described. Addressing the items highlighted below should help in the design and implementation of similar projects.

- Research partnerships can be used to leverage cutting edge science and biotechnologies. However, partnerships is not easy as problems that afflict developing countries are usually not on the radar of scientists in advanced research institutions.
- Collaboration between the groups was managed at the outset by material transfer and intellectual property right agreements. Patents on the antigens that were identified have been assigned to ILRI thereby safeguarding their eventual use in a commercial product.
- The ability to acquire and sustain funding for this type of research which often falls into the category of 'orphan' research is challenging.
- The perspective and experience of a commercial sector partner helped to focus the research agenda and multiple research options within the project were guided by predefined stop-go decisions.

Conclusion

Important progress has made in the process of developing a subunit vaccine against ECF by using a combination of genomics research and high throughput assays. This approach can significantly reduce the research time-frame for antigen identification and could be applied to jump-start other vaccine development programmes relevant to developing countries. The second phase of vaccine development, namely priming of protective immune responses remains a challenge and unfortunately is still very much driven by empirical principles. This situation should change as we acquire more detailed understanding of the molecular events underlying this process.

Studying the biology of an organism in the absence of its genome sequence is a handicap and understanding genomic and related technologies is essential if we are to empower scientists in developing countries to undertake modern molecular studies and to take advantage of the genomics revolution. These research disciplines will allow us to identify genes that will provide new solutions to problems in biology that will have a positive impact on human health, agriculture and the environment.

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References

1. Gardner, M. J., Bishop, R., Shah, T., de Villiers, E., Carlton, J. M., Hall, N., Ren, Q., Paulsen, I. T., Pain, A., Berriman, M., Wilson, R. J. M., Sato, S., Ralph, S. A., Mann, D. J., Xiong, Z., Shallom, S. J., Weidman, J., Jiang, L., Lynn, J.,Weaver, B., Shoaibi, A., Domingo, A. R., Wasawo, D., Crabtree, J., Wortman, J. R., Haas, B., Angiuoli, S. V., Creasy, T. H., Lu, C., Suh, B., Silva, J., Utterback, T.R., Feldblyum, T.V., Pertea, M.,

Allen, J., Nierman, W. C., Taracha, E., Salzberg, S. L., White, O. R., Fitzhugh, H. A., Morzaria, S., Venter, J.C., Fraser, C. M., and Nene, V. 2005. Genome sequence of *Theileria parva*, a bovine pathogen that transforms lymphocytes. *Science*. 309: 134-137.

2. Graham, S. P., Pellé, R., Honda, Y., Mwangi, D. M., Tonukari, N. J., Yamage, M., Glew, E. J., de Villiers, E. P., Shah, T., Bishop, R., Abuya, E., Awino, E., Gachanja, J., Luyai, A. E., Mbwika, F., Muthiani, A. M., Ndegwa, D. M., Njahira, M., Nyanjui, J. K., Onono, F. O., Osaso, J., Saya, R. M., Wildmann, C., Fraser, C. M., Maudlin, I., Gardner, M. J., Morzaria, S. P., Loosmore, S., Gilbert, S. C., Audonnet, J-C., van der Bruggen, P., Nene, V. and Taracha, E. L. N. 2006. Theileria parva candidate vaccine antigens recognized by immune bovine cytotoxic T lymphocytes. Proc. Natl. Acad. Sci. 103: 3286-3291.
3. Liolios, K., Tavernarakis, N., Hugenholtz, P., and Kyrpides, N. C. 2006. The Genomes On Line Database (GOLD) v.2: a monitor of genome projects worldwide. Nucl. Acids Res. 34: D332-334.
4. Morrison I.W., Taracha E.L., McKeever DJ. 1995. Theileriosis: progress towards vaccine development through understanding immune responses to the parasite. Vet. Parasitol. 57:177-187.
5. Mukhebi A.W., Perry B.D., Kruska R. 1992. Estimated economics of theileriosis control in Africa. Prev. Vet. Med. 12: 73-85.
6. Norval R.A.I., Perry B.D., Young A.S. 1992. The epidemiology of theileriosis in Africa. London: Academic Press.
7. Radley D.E., Irvin A.D., Cunningham M.P., Young A.S. editors. 1981. Infection and treatment method of immunization against theileriosis. The Hague: Martinus Nijhoff; p.227 Advances in the control of theileriosis.
8. Sullivan, C. B., Diggle, M. A., and Clarke, S. C. 2005. Multilocus sequence typying: Data analysis in clinical microbiology and public health. Mol. Biotechnol. 29: 245-254.
9. Tripathi, R. P., Mishra, R. C., Dwivedi, N., Tewari, N. and Verma, S. S. 2005. Current status of malaria control. Curr. Med. Chem. 12: 2643-2659.
10. Wack, A. and Rappuoli, R. 2005. Vaccinology at the beginning of the 21st century. Curr. Opin. Immunol. 17:411-418.

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Starvation, Obesity or Optimized Diets: Which Way for Nutrition?

Malcolm Elliott, Albert Sasson and Andrew Cockburn

Introduction

Of all the inequities in the world population, one of the most marked hinges on nutrition. Out of the global population of 6.65 billion, some 850 million people are starving while 1.3 billion are clinically overweight or obese. Starvation and obesity coexist in the same countries. Surprisingly, obesity is increasing faster in the developing world than in high-income countries. This is a serious global problem. The predicted increase in deaths from related non-communicable diseases will add a major burden to overstretched health services. Improved diets and nutrition are necessary to counteract diseases associated with metabolic syndrome, such as insulin resistance, as well as some cancers and osteoporosis. A holistic approach is needed not only to ensure basic food security, but also to optimize diets for health promotion and non-communicable disease prevention. Advances in genomics are enabling the improvement of crops via genetic enhancement, and will also facilitate improvements in health through a better appreciation of phenotypic variation due to genotype and diet. This field of nutrigenomics recognizes that individuals' diets should be uniquely tailored to their own genetic profiles.

The green revolution (Borlaug, 1970) boosted global food production at the rate of 2.8 per cent per annum between 1966 and 1990, while the world population grew at the rate of 2.2 per cent per annum (Kendall and Pimentel, 1994). However, these trends subsequently reversed. Between 1990 and 1997, the global population swelled by 1.7 per cent a year while the figure for food production was just 1.2 per cent (Borlaug, 1997). Meanwhile, some 850 million people are still starving. By 2025, the combination of population increases and shifts in eating habits is likely to increase food grain requirements by 70 per cent (Leisinger et al., 2002). However, there is little additional land available for food production (Borlaug, 2004). In short, it will be necessary to produce more food from less land, with less water, less labour, less fuel and fewer applications of agrochemicals, if humankind is to avoid even more serious food shortages this century (Swaminathan, 2000).

It is a matter of profound concern that in parallel with this crisis, a staggering 1.3 billion of the world's 6.65 billion people are now clinically overweight or obese, according to the World Health Organization (WHO). If this trend continues, the figure is likely to rise to some 1.5 billion by 2015. Obesity is not just an issue for developed countries. In fact, the WHO's latest estimates reveal that more than 75 per cent of women over 30 are overweight in countries as diverse as Barbados, Egypt, Malta and South Africa as well as in the US. Similarly, 75 per cent of men are overweight in countries ranging from Argentina to the UK.

This paradox, where starvation and obesity can even coexist in the same countries, reflects major changes in diet and physical activity patterns around the world. Key findings include evidence of a rapid rise in demand and consumption of edible oils, refined sugars and other calorific sweeteners as well as animal-derived foods. Most of these trends are related to higher income and urban living. Related changes in physical activity include a shift away from activities that use a lot of energy such as farming, mining and forestry, and towards less physical forms of employment — as well as changes in modes of transportation. A particularly worrying trend is the fact that levels of weight and obesity are increasing faster in the developing world than in high-income countries. And in all cases there is a particularly high prevalence in obesity among adolescents, which has been shown to persist into adulthood.

The likely increase in deaths from non-communicable diseases related to overweight and obesity will add a major burden to overstretched and often failing or embryonic health services. To place this in perspective, it is increasingly recognised that diet and nutrition are a key component of any preventative health strategy aimed at counteracting diseases such as those spanned by metabolic syndrome, including obesity, insulin resistance, hyperlipidaemia and hypertension. Metabolic syndrome greatly increases the chances of developing type 2 diabetes and coronary heart disease. Moreover, some cancers and osteoporosis are also linked to diet.

Towards the Evergreen Revolution

If, as many now think, humankind can only avoid mass starvation in this century by producing more food from less land, with less water, less labour, less fuel and fewer applications of agrochemicals, it must deliver an 'evergreen revolution' (Swaminathan, 2000). It will be necessary fully to exploit cutting-edge advances in plant science, such as those in genomics and crop gene manipulation, to facilitate the production of crop varieties that have higher yield potential, resistance to diseases and insects, and tolerance to stresses such as drought, salinity and unfavourable temperatures (Sasson and Elliott, 2004). Biotechnology has been and will continue to be a vital tool for addressing the problems of hunger and malnutrition. Khush and Ma (2004) have provided several examples.

Increasing the productivity of world agriculture

To increase crop productivity, crop cultivars with higher yield potential, greater yield stability and higher production efficiency are needed. Conventional hybridization and selection is the time-tested strategy for developing crop cultivars with higher yield potential, but such conventional methods are increasingly being supplemented with biotechnological techniques. These include molecular marker aided selection and the introduction of cloned novel genes into crop cultivars. For example, the efficiency of photosynthesis may be increased by improving the control of water loss from the leaves of cereals through regulation of stomatal opening and closing (Mann, 1999). Other researchers are trying to alter

the photosynthesis of rice from the C3 to the C4 pathway by introducing cloned genes from C4 maize, which regulate the production of enzymes responsible for C4 biosynthesis (Ku et al., 1999), (Matsuoka et al., 2001). If they are successful, the yield potential of rice may increase by 30-40 per cent.

Starch biosynthesis plays a pivotal role in plant metabolism, both as a transient storage metabolite in leaf tissue and as an important energy and carbon reserve for organs such as seeds, roots, tubers and fruit. Several enzymatic steps are involved in starch biosynthesis in plants. ADP-glucose pyrophosphorylase (ADPGPP) is a crucial enzyme in the regulation of starch biosynthesis in plant tissues. Even in storage organs with high levels of ADPGPP, its activity is still limiting. It should be possible to affect starch production in storage tissues positively by regulating the expression of the gene encoding this enzyme (Kishore, 1994). Starch levels and dry matter accumulation were enhanced in potato tubers of plants transformed with the glg^{c16} gene from *Escherichia coli* that encodes ADPGPP (Stark et al., 1992). The transformed potato plants had tubers with higher dry-matter and starch levels under both growth chamber and field conditions.

Increasing yield stability

Generally speaking, the full yield potential of crops is not realized because of the toll taken by diseases and insect pests, which in cereal crops are estimated to cause yield losses of up to 25 per cent annually. In 1998, Africa lost 60 per cent of its cassava crop to cassava mosaic virus. Sweet potato yields in many African nations have also fallen drastically, with some farmers losing up to 80 per cent of expected yields due to sweet potato weevils and feathery mottle virus. Similarly, crop yields are reduced and fluctuate greatly as a result of abiotic stresses such as drought, excess water, mineral deficiencies and toxicity in soil, and abnormal temperatures. Genetically improving crops to withstand biotic and abiotic stresses can help build yield stability and contribute to increased food security.

The logical approach to minimizing crop losses from pest attack is conferring better resistance in the host. This is happening, with numerous cereal crop varieties engineered to have multiple resistance, for instance. Biotechnology applications have opened new vistas for developing crop cultivars with durable resistance. As in industrialized countries, the focus

has been on incorporating Bt genes for protection against insects. So far there have been promising developments. Bt-containing maize strains have been approved for commercial production in the Philippines, and Bt-containing rice has been developed in several Asian countries and is undergoing field trials in China. Efforts are also underway to develop sweet potatoes with resistance to feathery mottle virus as well as beans, cassava and other staples with resistance to other viruses.

Molecular marker aided selection is being used to enhance the efficiency of selection in crop improvement. For example, useful genes when tagged with molecular markers can be moved from one varietal background to another more efficiently. Tagged genes can be pyramided (a technique also known as 'gene stacking') to develop durable resistance to a wider spectrum of diseases or insects. One researcher (Huang et al., 1997) pyramided four genes for resistance to bacterial blight of rice through molecular marker aided selection.

Aside from improved productivity, genetically modified plants have other important benefits for farmers in developing countries. For example, in China, where pesticides are typically sprayed on crops by hand, some 400 to 500 cotton farmers were dying every year from acute pesticide poisoning. Planting transgenic cotton with the Bt gene resulted in a reduction in pesticide use of more than 75 per cent, and lowered the number poisoned by pesticides by an equivalent amount (Huang et al., 2002). The Consultative Group on International Agricultural Research (CGIAR) estimated that, with improvement of traits like these through biotechnology, world food production could be boosted by up to 25 per cent (Kendall et al., 1997).

Progress in developing crop cultivars for tolerance to abiotic stresses such as drought has been slow because of a lack of knowledge about the mechanism of tolerance, poor understanding of the inheritance of resistance, low heritability, and a dearth of efficient techniques for screening the germplasm and breeding materials. Genetic engineering techniques hold great promise for developing crop cultivars with higher levels of tolerance to abiotic stresses. These traits would be tremendously advantageous to poor farmers in developing countries, especially in Africa.

It has been shown, for example, that tropical crops can be modified to better tolerate acidic soils (de la Fuente et al., 1997). It is known that

many wild species tolerant of such soils produce citric acid, so plants were genetically engineered to overproduce citric acid in root exudates, which helped make them tolerant of aluminium toxicity, a common problem throughout the tropics. The high level of citric acid acted to chelate aluminium in the rhizosphere and prevent its entry into the roots. The presence of citric acid in the rhizosphere also boosted the availability of calcium, magnesium and iron, which are normally deficient in acid soils.

Tackling the problems of malnutrition

Organizations concerned with human nutrition, such as the World Health Organization (WHO) and more recently the Consultative Group on International Agriculture (CGIAR), have made fighting the 'hidden hunger' — micronutrient deficiencies — a high priority (Bouis et al., 2000). Micronutrient deficiencies affect some three billion people, or half the world population. The target micronutrients are iron, zinc and vitamin A because these are often massively deficient among the world's poor.

A rice improvement project at the International Rice Research Institute (IRRI) in the Philippines aims to develop improved rice cultivars with high levels of iron and zinc through conventional hybridization and selection (Khush, 2001). Biotechnological approaches are also proving effective in raising the iron content of rice. One team (Goto et al., 1999) transferred the soybean *ferritin* gene into the rice variety kita-ake through *Agrobacterium*-mediated transformation, bumping up the iron content up to three times that of controls. Another team meanwhile introduced the *ferritin* gene from the common bean into rice, and the transgenic lines had double the amount of iron as controls (Lucca *et al.*, 2001). To increase the bioavailability of iron, this team also introduced the thermotolerant phytase gene from a fungus into rice endosperm.

Getting enough beta-carotene (the precursor of vitamin A) — a micronutrient vital for healthy vision and normal growth and development — is very important in rice-dependent countries. As it does not occur naturally in the endosperm of rice, people deriving most of their calories from rice suffer from vitamin A deficiency; and in Vietnam, Laos, Cambodia, Nepal, Bangladesh and India, poor people derive more than 60 per cent of their calories from rice. So a genetic engineering project to introduce the biosynthetic pathway leading to the production of beta-

carotene in rice endosperm was implemented by a team in Switzerland (Ye et al., 2000).

Two genes from the daffodil and one from a bacterium (*Erwinia uredovora*) were introduced into the model rice variety Taipei 309. Ten plants had beta-carotene in their endosperm, a normal vegetative phenotype and were fully fertile. Taipei 309 was used to introduce the beta-carotene biosynthetic pathway, as it is easy to transform. However, it is no longer cultivated due to its low yield potential. Another team (Hoa et al., 2003) have introduced the same genes into indica and japonica lines amenable to deregulation.

Biotechnology approaches are also being used to enhance the lysine content of corn, soybean and rapeseed. The introduction of two bacterial genes for dihydrodipicolinic acid (DHPHS) and aspartokinase (AK) enzymes encoded by *dap A* gene from *Corynebacterium* and lysC gene from *Eschericha coli* led to a fivefold increase of lysine in corn, soybean and rapeseed (Falco et al., 1995).

A Deeper Understanding of Obesity

Hunger and deficiencies are just one side of the current global crisis in nutrition. Obesity has reached such epidemic proportions internationally that world health officials have been taking an aggressive approach to the matter in the hope that they will be able to prevent a global explosion of fat-related diseases. Obesity, diabetes and heart disease — commonly thought to be afflictions of the affluent — have spread to the developing world, even to regions suffering from malnutrition. In fact, in some parts of Africa, overweight and obesity afflict more children than malnutrition —— in some cases, four times as many.

In Egypt more than 25 per cent of 4-year-olds are fat, and obesity rates are also more than 25 per cent among children aged between 4 and 10 in Chile, Peru and Mexico. In some countries, more than 30 per cent of the children are obese. The WHO believes that the consumption of junk food must be reduced, but it is not approaching the issue as aggressively as it has tackled tobacco smoking. Instead it has urged food producers to change their advertising to promote physical activity and emphasize the benefits of less salty, less sugary, less fatty foods.

It seems that there may, in fact, be a genetic predisposition to obesity in some individuals. An international team of scientists led by researchers in the genetics and genomics department at Boston University School of Medicine have identified a common genetic variant, present in 10 per cent of the people studied, associated with an elevated risk of obesity in both adults and children of European and African ancestry (*Science*, 14 April, 2006).

The variant was identified by examining over 100,000 single nucleotide polymorphisms (SNPs) in each individual in DNA samples from participants in the Framingham Heart Study. The Boston team analyzed the genetic variation using Affymetrix GeneChip® Mapping 100K DNA microarray technology.

The study used measurements of body mass index of the study participants that had been gathered over 24 years. The team then performed a genome-wide analysis to identify the common genetic variants associated with obesity, which led to the discovery of a variant near the INSIG2 gene (insulin-induced-gene 2). The Boston team also collaborated with researchers from other laboratories in the US and in Germany.

The studies revealed that the 10 per cent with the common genetic risk factor were heavier and showed a higher risk of becoming obese, regardless of sex and age. The association was also observed in children and adolescents. In many cases a predisposing genetic signature such as this one may also require a specific environment to show its effects. Roughly half of obesity risk is genetically determined, and the remainder is due to environmental factors such as diet and exercise. Obesity is also a risk factor for many common diseases such as type 2 diabetes, heart disease, hypertension, stroke and some cancers.

Nutrigenomics: Fuelling Our Future

Genomics is increasingly used for improved plant breeding via genetic enhancement; and the same technology is also of strategic importance in the task of improving the health and well-being of people through a better appreciation of phenotypic variation due to genotype and diet. Ultimately a better knowledge of the human genome and the function of genes could help prevent potentially major epidemics of non-communicable disease

and disorders by making it possible to tailor diets to the specific demands of a person's own or at least their culture's own genetic profile. This new field of "nutrigenomics" (see Box, **Nutrigenomics in summary**) involves the application of the sciences of genomics, transcriptomics, proteomics and metabolomics to human nutrition, especially the relationship between nutrition and health.

Nutrigenomics in summary

Nutrigenomics is the application of the sciences of genomics, transcriptomics, proteomics and metabolomics to human nutrition. It focuses on the relationship between genotype, phenotype, nutrition and health. Disease prevention is possible by optimising dietary choices according to one's genetic constitution (you are what you eat and you eat what you are). This requires understanding, and ultimately modulating (via bespoke, individually optimised diets and plant breeding), a multitude of nutrient-related interactions at the gene, protein and metabolic levels. It is a new field: its technologies and optimised diets will shift health provision from reactive to proactive with attendant individual benefits.

Broccoli, which contains glucosinolates — substances believed to have considerable health benefits — provides one example of the way in which nutrigenomics may be exploited to optimize one element of the diet of an individual who is potentially at risk. It seems that consumption of high-glucosinolate broccoli can lead to activation of a suite of tumour suppressor genes, a phenomenon that can be shown using gene chip technology. Once the evidence is found to be sufficiently robust, it will be possible to consider human intervention trials (with ethical approval). It would then be necessary to demonstrate health benefits in genetically indicated high-risk groups. The modified broccoli could then be registered under EU Health Claims Regulations which are currently being developed, and the product, with real potential individual benefits, would sell at a premium.

Conclusion

To ensure basic food security for all, and to optimize diet as a next major goal for promoting health and preventing non-communicable disease, a holistic approach is necessary. Governments are becoming ever more aware of this connection, elegantly expressed by Hippocrates, the father of modern medicine, 2,500 years ago as "let food be thy medicine and medicine be thy food".

So in addition to exploiting our increasing understanding of genomics for improved plant breeding via genetic enhancement, the same technology is also of strategic importance for improving the health and well-being of people through a better appreciation of phenotypic variation due to genotype and diet. Dietary prevention of potentially major epidemics of non-communicable disease and disorders may benefit strongly from nutrigenomics, which recognises that individuals' diets should be uniquely tailored to the specific demands of their own or at least their cultures' genetic profiles.

This interplay between certain cultures and certain diets, suggesting some interplay of genes and nutrition, is amply demonstrated by a range of examples. For instance, the Inuit of Alaska, whose metabolism was suited to high daily energy expenditure and high fat-food, are now suffering the consequences of 'Western-style' living, whereas the Japanese who relocated to the US after the second world war found that their cholesterol levels soared and the Maasai of East Africa have developed health problems since abandoning their traditional meat-based diet.

There is an old medical saying that we dig our grave with our spoon. The paradox of living in a world where nutrition is increasingly askew, and obesity and hunger often coexist in the same country, must be solved with a new middle road where the spoon is neither too empty nor too full.

References

1. Borlaug, N.E. 1970. The green revolution — peace and humanity (Nobel Peace Prize Lecture). CIMMYT, Mexico City, Mexico. Available at: www.agbioworld.org/biotech_info/topics/borlaug/nobel-speech.html)

2. Borlaug, N.E. 1997. Feeding a world of 10 billion people: the miracle ahead. Plant Tissue Culture and Biotechnology. Vol. 3, pp 119-127
3. Bouis, H.E., Graham, R.D. and Welch, R.M. 2000. The CGIAR micronutrient project: justification, history, objectives and summary of findings. In Workshop on improving human nutrition through agriculture: the role of international agricultural research. Vol. 21, pp 374-381
4. De la Fuente, J.M. et al., 1997. Aluminium tolerance in transgenic plants by alteration of citrate synthesis. Science. Vol. 276, pp 1566-1568
5. Falco, S. C. et al., 1995. Transgenic canola and soybean seeds with increased lysine. Biotechnology. Vol. 13, pp 577-582
6. Huang, N. et al., 1997. Pyramiding of bacterial blight resistance enes in rice: marker-aided selection using RFLP and PCR. Theoretical and Applied Genetics, Vol. 95, pp 313-320
7. Kendall, H.W. et al., 1997. Bioengineering of crops: report of the World Bank Panel on Transgenic Crops. World Bank, Washington DC
8. Kendall, H.W. and Pimentel, D. 1994. Constraints on the expansion of the global food supply. Ambio. Vol. 23, pp 198-205
9. Khush, G. S. 2001. Challenges for meeting the global food and nutrient needs in the new millennium. Proceedings of Nutrition Society. Vol. 60, pp 15-26
10. Khush, G. and Ma, J. 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, UK, pp 1313-1320
11. Ku, M.S.B. et al., 1999. High-level expression of maize phosphoenolpyruvate carboxylase in transgenic rice plants. Nature Biotechnology. Vol. 17, pp 76-80
12. Leisinger, M, C. Schmitt, and Pandya, L. 2002. Six billion and counting, population and food security in the 21st century. International Food Policy Research Institute, Washington DC
13. Lucca, P., Hurrell, P. and Potrykus, I. 2001. Genetic engineering approaches to improve the bioavailability and level of iron in rice grains. Theoretical and Applied Genetics. Vol. 102, pp 392-397
14. Mann, C.C. 1999. Genetic engineers aim to soup up crop photosynthesis. Science. Vol. 283, pp 314-316
15. Sasson, A. and Elliott, M.C. 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, UK, pp 1201-1205
16. Stark, D.M. et al., 1992. Regulation of the amount of starch in plant tissues by ADP glucose pyrophosphorylase. *Science*. Vol. 285, pp 287-292
17. Swaminathan, M. S. 2000. An evergreen revolution. Biologist. Vol. 47, No. 2, pp 85-89
18. Ye, X. S. et al., 2000. Engineering the provitamin A (beta-carotene) biosynthetic pathway into (carotenoid-free) rice endosperm. Science. Vol. 287, pp 303-305

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Strategies for Plant Breeding: Affordable and Effective

Eric Huttner, Vanessa Caig, Jason Carling, Margaret Evers, Neil Howes, Grzegorz Uszynski, Peter Wenzl, Ling Xia, Shiying Yang, Ange-Marie Risterucci and Andrzej Kilian

Introduction

Over the past 20 years, DNA-based technologies have been successfully applied to plant improvement, in two different ways. First, using recombinant DNA techniques and plant transformation methods, transgenic (GM) crops have been developed and are now commonly grown in many countries. These crops have been successful only for a small number of genetically simple traits so far. Not more than a handful of useful genes have been deployed on a significant scale, in only four major crops of economic importance in the developed world (James, 2005). Second, polymorphic DNA markers have been identified in many species. Using suitable genotyping methods, these markers can be applied to plant breeding: they assist breeders in characterising their germplasm. Once an association between a polymorphic marker and a useful trait is discovered, the marker can be used to accelerate breeding by replacing slow, expensive and/or unreliable phenotypic assays of useful traits. Molecular marker-assisted breeding has now been used extensively for a

limited number of traits, mostly in a small number of major crops grown in developed countries. Any crop in any country would potentially benefit from molecular marker-assisted breeding. However, with the common marker systems in use today, marker technology use remains limited. The widespread adoption of marker-assisted breeding, especially in orphan crops, is constrained by the cost of marker discovery and the high cost and low throughput of genotyping once markers have been discovered. These obstacles limit the density of markers covering the genome of most crops where markers are available. For minor, under-resourced, subsistence crops, markers are sometimes not available at all.

Over the past six years we have established Diversity Arrays Technology (DArT), a new marker system, which allows the establishment and production of cost-effective whole-genome profiles for most crops. The technology has been described extensively in the scientific literature: Jaccoud et al., 2001, Wenzl et al., 2004, Kilian et al., 2005, Xia et al., 2005, Wittenberg et al., 2005, Yang et al., 2006, Akbari et al., 2006, Wenzl et al., 2006. The technology is also described on the web site www.DiversityArrays.com and was presented at BioVision Alexandria 2004 (Huttner et al., 2005).

In this paper, we present two examples of the development, delivery, and applications of DArT markers.

Delivery of DArT Profiles in Wheat

DArT was established in hexaploid (bread) wheat in 2004 (Akbari et al., 2006). Following an extensive discovery phase during which about 12,000 bread wheat clones were screened for polymorphism, we identified a collection of about 2,500 markers. Based on these markers, a "DNA to data" wheat genotyping service was established by Triticarte Pty Ltd (www.triticarte.com.au). Triticarte has been producing data since February 2005. Over the 12 months from March 2005 to February 2006, we analysed 48 populations of various sizes, sent by wheat researchers from Australia and five other countries. The populations comprised mapping populations and diversity populations. Using mapping populations, researchers and breeders try to identify genetic linkage between a trait and one or several

molecular markers. The construction of many genetic maps and their alignment against each other allowed us to assign most DArT markers to chromosomes, showing that the available markers provide good coverage of the genome (Table 1). Results from the diversity populations allow breeders to recognize relatedness between lines and to manage their germplasm collections better. Some statistics about the data produced are presented in Table 2. Clearly, the density of the genome profiles produced is adequate for most application in wheat genetics and breeding.

Table 1. Distribution of DArT markers in the wheat genome

Chromosomes ->Genome	1	2	3	4	5	6	7
A	94	95	111	185	81	139	124
B	165	172	194	59	125	192	158
D	78	91	72	22	24	32	86

Table 2. Wheat data produced by Triticarte (March 2005 to February 2006)

	Minimum	Maximum	Average	Standard Deviation
Samples analysed for 28 mapping populations	24	257	122	61
Markers reported for 28 mapping populations	178	688	358	121
Samples analysed for 20 diversity populations	10	741	113	157
Markers reported for 20 diversity populations	311	1404	686	250

Establishment of DArT in Banana

Fruit from plants of the genus Musa is one of the world's most important crop with 73 million metric tonnes of banana and 33 million metric tonnes of plantains produced in 2005. Cultivated banana originates from the domestication of interspecific crosses between four wild Musa species. These species contributed genome A (*Musa acuminate*), B (*Musa balbisiana*), S (*musa schizocarpa*) and T (*Musa autralimusa*), resulting in diploid cultivars selected for parthenocarpy and sterility. Triploid cultivars were then obtained. The most widely used cultivars have genome structure AA (Figue sucrée), AAA (Dessert banana, Cavendish), AAB (Plantain, Figue pomme) and ABB (Dessert cooking). Whole-genome molecular marker profiles would be very useful to understand the structure and evolution of the Musa genome(s). One objective of project 4 (Assessing DArTs as a genome-wide scanning technology) in Subprogram 2 of the Generation Challenge Program was the development of a DArT genotyping array for banana. We have now established two libraries of 6,000 DArT clones using the same complexity reduction method as for wheat and barley, based on restriction enzymes *Pst*I as a primary cutter and *Taq*I or *Bst*NI as a secondary cutter. Between 700 and 800 markers were identified in these libraries. Initial analysis of 48 diverse banana and plantain accessions showed that while the majority of the markers separated the A and the B genome, the array could also resolve diversity within each genome. Furthermore, the array could identify genetic heterogeneity in clonal material. The technology is now in place for large scale diversity analysis and collection management, genetic mapping and marker-trait association studies.

Future Applications of Whole-Genome Profiles

The availability of affordable whole-genome profiles will assist plant breeders in many areas. The comprehensive profiles provide a high resolution, single-step characterisation of the germplasm. They allow efficient genetic background screening in back-crosses, therefore accelerating the introgression of useful traits from exotic germplasm. Thanks to the profile density, multiple regions responsible for complex

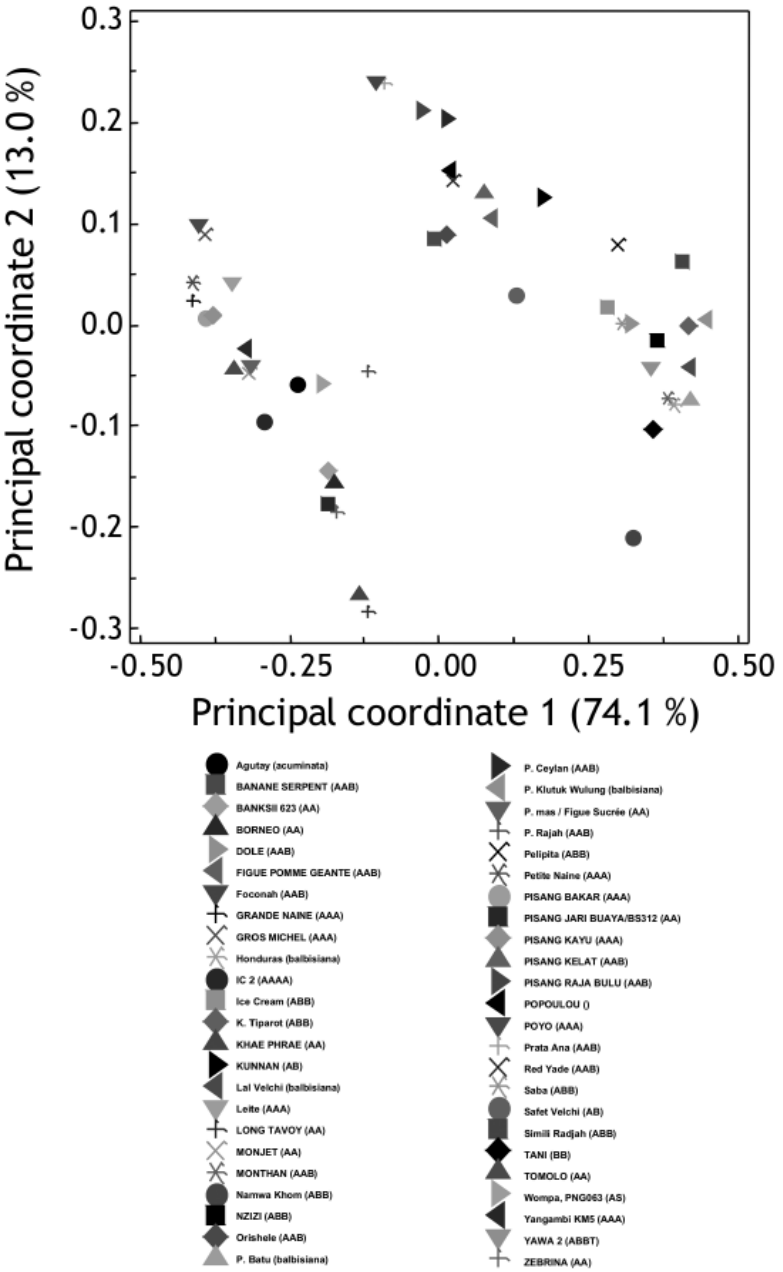

Figure 1. Diversity analysis of 48 banana and plantain cultivars based on 332 DArT markers

A set of 48 diverse banana and plantains samples used in the initial array construction was analysed on the PstI/TaqI DArT array. Scores for the highest quality 332 markers were used in a Principal Coordinate Analysis. The array separates clearly the A and the B genomes (principal coordinate 1). The array also resolves differences within each genome principal.

traits can be identified by QTL analysis or by association mapping and multiple traits can be selected for simultaneously.

It has been well documented that genetic progress can be accelerated by using exotic germplasm (for example Frary et al. 2003, Thomson et al. 2006). At the same time, introducing exotic alleles while retaining the adaptation complexes underpinning the agronomic and quality attributes of elite varieties has been a challenge. Molecular markers improve the efficiency of the introgression process. The high density profiles obtained using DArT provide the breeders with the tool they need to productively harness exotic genetic diversity and may relieve a limitation of this approach to plant breeding.

So far, marker-trait association studies have been based on the laws of quantitative genetics. Recent progress in data mining algorithms, for example those developed to study transcriptomes (Tothill et al. 2005), open a new way to examine the "data-rich" whole genome profiles we can now efficiently produce. Whether such novel approaches will result in the discovery of new marker-trait associations remains to be seen, but the availability of the data now makes this strategy possible.

Conclusion

DArT provides affordable whole genome profiles for many crop species. Based on past successes, we believe that DArT can be quickly and cost-effectively established for any plant species. The profile density is suitable for most research and breeding applications. Further development in breeding methods and software will increase the application of comprehensive genome profiles.

Acknowledgements

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References

1. Akbari M., Wenzl P., Vanessa C, Carling J., Xia L., Yang S., Uszynski G., Mohler V., Lehmensiek A., Kuchel H., Hayden M.J., Howes N., Sharp P., Rathmell B., Vaughan P., Huttner E. and Kilian A. (2006) Diversity Arrays Technology (DArT) for high-throughput profiling of the hexaploid wheat genome. Theoretical and Applied Genetics, in press.
2. Frary A., Doganlar S., Frampton A., Fulton T., Uhlig J., Yates H. and Tanksley S. (2003) Fine mapping of quantitative trait loci for improved fruit characteristics from Lycopersicon chmielewskii chromosome 1. Genome. Vol. 46, No 2, pp 235-243.
3. Huttner E., Wenzl P., Akbari M., Caig V., Carling J., Cayla C., Evers M., Jaccoud D., Peng K., Patarapuwadol S., Uszynski G., Xia L., Yang S. and Kilian A. (2005) Diversity Arrays Technology: A novel tool for harnessing the genetic potential of orphan crops. In Serageldin, I. and Persley, G. J. (eds) Discovery to Delivery: BioVisionAlexandria 2004, Bibliotheca Alexandrina, El-Shatby-Alexandria 21526, Egypt. www.bibalex.org/bioalex2004conf.
4. Jaccoud D., Peng K., Feinstein D. and Kilian A. (2001) Diversity Arrays: a solid state technology for sequence information independent genotyping. Nucleic Acids Research. Vol. 29: e25.
5. James, C. 2005. Global Status of Commercialized Biotech/GM Crops: 2005. ISAAA Briefs No. 34. ISAAA: Ithaca, NY.
6. Kilian A., Huttner E., Wenzl P., Jaccoud D., Carling J., Caig V., Evers M., Heller-Uszynska K., Cayla C., Patarapuwadol S., Xia L., Yang S. and Thomson B. (2005) The fast and the cheap: SNP and DArT-based whole genome profiling for crop improvement. In Tuberosa R., Phillips RL. and Gale M. (eds) Proceedings of the International Congress "In the Wake of the Double Helix: From the Green Revolution to the Gene Revolution", May 27-31, 2003, Avenue media, Bologna, Italy, 443-461.
7. Thomson M.J., Edwards J.D., Septiningsih E.M., Harrington S.E. and McCouch S.R. (2006) Substitution mapping of dth1.1, a flowering time QTL associated with transgressive variation in rice, reveals multiple sub-QTLs. Genetics. Vol. 172, No. 4, pp 2501-2514
8. Tothill R., Kowalczyk A., Rischin D., Bousioutas A., Haviv I., van Laar R.K., Waring P.M., Zalcberg J., Ward R., Biancan A., Sutherland R., Fong K., Pollack J.R., Bowtell D.D.L. and Holloway A.J. (2005) An expression-based site of origin diagnostic for clinical application to cancer of unknown primary. Cancer Research Vol. 65, No. 10, pp 4031-4040.
9. Wenzl P., Carling J., Kudrna D., Jaccoud D., Huttner E., Kleinhofs A. and Kilian A. (2004) Diversity arrays technology (DArT) for whole-genome profiling of barley. Proceedings of the National Academy of Sciences. Vol. 101, pp 9915-9920.

10. Wenzl P., Li H., Carling J., Zhou M., Raman H., Paul E., Hearnden P., Maier C., Xia L., Caig V., Ovesná J., Cakir M., Poulsen D., Wang J., Raman R., Smith K.P., Muehlbauer G.J., Chalmers K.J., Kleinhofs A., Huttner E. and Kilian A. (2006) A high-density consensus map of barley linking DArT markers to SSR, RFLP and STS loci and agricultural traits, submitted to BMC Genomics.
11. Wittenberg A.H.J., van der Lee T., Cayla C., Kilian A., Visser R.G.F. and Schouten H.J. (2005) Validation of the high-throughput marker technology DArT using the model plant Arabidopsis thaliana. Molecular Genetics and Genomics. Vol. 274, pp 30-39.
12. Xia L., Peng K., Yang S., Wenzl P., de Vicente C., Fregene M. and Kilian A. (2005) DArT for high-throughput genotyping of cassava (Manihot esculenta) and its wild relatives. Theoretical and Applied Genetics. Vol. 110, pp 1092-1098.
13. Yang S., Pang W., Ash G., Harper J., Carling J., Wenzl P., Huttner E. and Kilian A. (2006) Low level of genetic diversity in cultivated pigeonpea compared to its wild relatives is revealed by Diversity Arrays Technology (DArT). Theoretical and Applied Genetics, in press.

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Technology Transfer in Agribiotech: The Case of Asia's Eggplant

Frank Shotkoski

Introduction

For new technologies to be accepted in the developing world, local people need to be consulted first about their needs — a simple and pragmatic fact not lost on the Agricultural Biotechnology Support Project II. A consortium funded by the United States Agency for International Development (USAID) and led by the US-based Cornell University, the ABSPII works to bring the benefits of agricultural biotechnology to small-scale and resource-poor farmers and consumers in Africa and Asia.

The consortium supports agricultural research, policy formulation and regulatory systems in India, Bangladesh, Indonesia, the Philippines, Mali, Uganda and Kenya. ABSPII assists decision-makers in these partner countries to identify biotechnology solutions that are appropriate for the production constraints important domestic crops must operate under. They also facilitate partnerships among scientists in the private and public sectors to encourage the transfer of leading-edge biotechnology. Scientists in the consortium's partner countries are then able to use this technology to improve the productivity of local plant varieties.

The ABSPII has adopted a comprehensive approach to its work that emphasizes product development and delivery. Consulting local

stakeholders to determine their highest priority needs for agricultural products is always the first step. An early consultation has been found to be essential for local stakeholders to be interested enough to buy the product, and ensures that the ABSPII does not invest in technology that is unlikely to be adopted.

Next, the feasibility of developing and delivering the product is assessed. If the result is positive, the consortium then organizes its work into 'product commercialization packages' (PCPs) that integrate all elements of the research, development and commercialization processes, including:

- Development of the technology.
- Policy-related issues such as licensing the intellectual and technical properties associated with the product, as well as applying for and obtaining regulatory approval by the relevant national authorities.
- Providing public information to producers and consumers about the benefits, risks and correct management of the new products.
- Establishing, or verifying the existence of marketing and distribution mechanisms to provide farmers access to planting material.

Its strategy involves needs-based capacity building related to each set of activities. As the consortium is a non-profit organization, it can focus on crops whose limited market value may mean they are overlooked by multinational biotechnology companies, but which are extremely important to subsistence and resource-poor farmers. When applicable, ABSPII forms partnerships with local agricultural universities and private biotechnology and seed companies to conduct research and development activities necessary to bring the highest-quality product to farmers.

Whenever appropriate, ABSPII seeks opportunities to create public-private partnerships in industrialized and developing countries as a way of leveraging public funds, absorbing development costs, and providing a broader distribution channel. Many developing countries lack private seed enterprises or private companies to act as financial or distribution partners. But these can be key.

A case in point is the consortium's collaboration to commercialize insect-resistant eggplant, or aubergine, with the Maharashtra Hybrid Seed Company (Mahyco) in India. The benefits — especially in areas such as product stewardship, quality control and biosafety compliance — were legion. ABSPII thus feels it will be increasingly important to help

developing countries build their own plant breeding and seed production industries. More, it believes that the biotechnology-derived traits that are its focus will add value to an industry with historically low value, providing impetus for entrepreneurs to come forward.

Engineering a Better Eggplant

Eggplant is one of the most nutritious and culturally important vegetables in South Asia. It is also highly vulnerable to one particular pest: the production of marketable eggplants is compromised by severe infestations of the eggplant fruit and shoot borer, which often reduces yields by up to 70 per cent, and can damage as much as 90 per cent of a crop.

To control the borer, farmers spray chemical insecticides as often as every other day. This threatens not only their own health but also that of consumers and the environment, increases production costs, and ultimately makes the vegetable more costly. Meanwhile, the insect is developing a tolerance to chemical pesticides, making it more difficult to control. Integrated pest management strategies are available that reduce borer infestation by up to 30 per cent, but these are not popular among farmers because of their complexity and high demand for labour.

In collaboration with the US biotechnology giant Monsanto, the Maharashtra Hybrid Seed Company (Mahyco) — a pioneering Indian firm — has developed a highly resistant transgenic eggplant. This was engineered to contain the Bt Cry1Ac gene, conventionally bred into 12 Mahyco eggplant varieties and hybrids to meet different regional preferences. Mahyco has also shared the technology with public institutions in India, Bangladesh and the Philippines to develop open pollinated varieties (OPVs).

Initial field trials comparing the Mahyco Bt hybrids against non-Bt hybrids indicate that farmers can expect a 45 per cent reduction in the use of chemical insecticides. Researchers also found higher yields on the Bt plots, with 45 tonnes per hectare versus only 22 tonnes on non-Bt plots. Once commercialized, Bt eggplant has the potential to benefit 700,000 farmers over these three countries, the majority of whom will be relatively poor smallholders.

Why Public-Private Partnerships?

We have seen how potentially profitable Bt eggplant can be. But the partnership that produced it is as important as the crop itself. Eggplant is delivered to high-value markets by the private sector, which is entrenched in producing hybrids, while resource-constrained farmers are provided with seeds by public institutions that have developed region-specific varieties. In India, for example, leading universities and public research institutions have developed region-specific commercial seeds from breeders' lines, and deliver these to farmers at cost. Over 60 per cent of farmers currently source their seeds from the public system.

Mahyco's Bt eggplant seeds will provide a solution to farmers currently engaged in cultivating hybrids. Meanwhile, the public-private partnership will allow public institutions to access Mahyco technology. This, in turn, will help thousands of poorer farmers to access high-quality, open-pollinated transgenic seeds and thereby enhance their income.

Since the private and public sectors cater to different segments of the market, there is little commercial conflict arising out of this partnership. Two streams of product development, one under the private sector and the other under the public, are expected to encourage more to grow the Bt eggplant, and address the critical issue of social equity in the commercialization process.

Sathguru Management Consultants, the coordinator for the ABSPII project in South Asia, negotiated the technology transfer arrangement under which Monsanto and Mahyco would transfer their technology to identified public institutions. The publicly developed and publicly produced FSB-resistant seeds are to be delivered to poorer farmers.

When choosing a public-sector partner, the public institution needs to have the ability to produce commercial seed from the breeder as well as foundation seed and adopt good manufacturing practices. So Sathguru has chosen public partners who have proven track records in producing and delivering seed to farmers.

The strategy is to ensure that the chosen public institutions are competent bodies that have capabilities throughout the seed production chain, that is, from breeder seed to foundation seed to commercial seed. An added element of this critical issue is the not-for-profit nature of sales while formulating the product delivery strategies for OPVs and also to

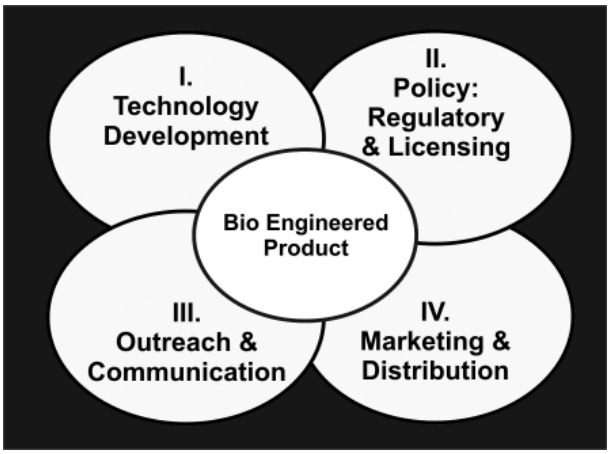

Figure 1. An Integrated Approach to Rural & Agricultural Development

ensure their ability to address responsibilities in delivering a genetically modified seed.

In the public domain, the Indian Institute of Vegetables Research (IIVR), Tamil Nadu Agricultural University (TNAU) and the University of Agricultural Sciences (UAS, Dharwad) have been chosen as they have the capability and infrastructure for seed development and multiplication for end use distribution. Dharwad has been producing and distributing truly certified seeds worth more than a million dollars a year. TNAU's CO varieties are very popular among Tamil Nadu farmers, and it multiplies and delivers CO varieties to farmers directly.

In the Philippines, IPB-UPLB has a proven track record of producing and distributing foundation and certified seed of OPVs and hybrids of various economically important crops, including vegetables, to poorer farmers and other users. IPB-UPLB also distributes IPB-bred varieties and hybrids through franchising agreements with the private sector. In Bangladesh, efforts will be taken to strengthen the capability of public institutions to deliver the seeds to farmers by encouraging the adoption of good manufacturing practices.

Further links for distribution through private enterprises could be important, but issues such as trademarks and royalties would need to be addressed if public institutions chose to deliver seeds to the farmers through a private partnership. These options have been taken note of

and, accordingly, technology transfer agreements have been developed providing for strategic options with related links for royalties and trademarks in case the public partners choose to deliver products through their private counterparts.

To ensure that the partners are adequately geared to absorb technologies and deliver products in the agreed manner, stewardship responsibility for technology management and overall project management rests with Sathguru. The Indian Agricultural Research Institute (IARI) has made considerable progress toward developing a transgenic Bt eggplant, but have encountered roadblocks in accessing the most effective Bt gene. Mahyco has a relationship with Monsanto that has enabled them to commercialize Bt hybrid cotton in India, completing all regulatory steps in 2002. For Bt eggplant, Mahyco will partner public sector organizations like TNAU, IIVR and UAS-Dharwad. The role of these public sector organizations is to backcross the identified locally popular varieties with the transgenic product developed by Mahyco to distribute transgenic OPV seeds through the well-established public seed distribution system prevailing in India.

The project would provide opportunities for important public institutions in India to access and acquire Bt technology and product delivery rights based on the Mahyco's Cry1Ac-based approved event. That would accelerate the biosafety timeline and bring many different products to market in the shortest possible time. A careful analysis has been carried out by partner institutions with the help of Sathguru to identify the most commonly grown varieties and varieties that are emerging as the preferred choice of farmers from among the myriad of varieties introduced by the public sector research institutions in India and Bangladesh.

This range of identified varieties will facilitate selection, by experienced breeders, of those most amenable to successful backcrossing. Based on the agronomic performance and molecular tests, these varieties will be narrowed down for commercialization for each of the regions.

Conclusion

The project reached an important milestone in India in July 2005 when Mahyco transferred fruit and shoot borer-resistant seeds to TNAU. Funded by USAID and led by Cornell University College of Agriculture and Life

Sciences' Office of International Programs (IPCALS), the ABSPII helps public universities and research institutions in developing countries gain access to technology developed in the private sector or at other universities around the world. The Mahyco-TNAU partnership is particularly rewarding because it is an excellent example of a 'homegrown' Indian seed company sharing technology with a public university. We expect this type of public-private cooperation to be a model for the development of agriculture biotechnology products in many other parts of the developing world.

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Better Rice for a Growing World

Gurdev Khush

Introduction

Rice is the world's most important food crop and a primary source of calories for more than half the world's population. More than 90 per cent of the world's rice is grown and consumed in Asia, where 60 per cent of the global population live. Rice accounts for up to three-quarters of the calories consumed by more than three billion Asians and rice paddies take up 11 per cent of the world's cultivated land.

Rice is also probably the most diverse crop on earth. It is grown as far north as Manchuria in China and as far south as Uruguay and New South Wales in Australia. Rice grows at elevations of more than 300 metres in Nepal and Bhutan, and 3 metres below sea level in Kerala, India. There are four major categories of rice-growing environment — irrigated, rainfed, upland and floodprone — based on criteria such as water regime during growing, drainage, soils and topography.

There have been major advances in food production over the last four decades. Between 1966 and 2000, the population of densely populated low-income countries grew by 90 per cent, but rice production increased by 130 per cent, from 257 million tons in 1966 to 600 million tonnes in 2000. In 2000, per capita food availability, on average, was 18 per cent higher than it was in 1966.

The technological advance that led to such dramatic achievements in world food production was the development of high-yield varieties of rice that are also insect and disease-resistant. Other green revolution elements in the successful mix included the development of irrigation facilities, the use of inorganic fertilizers and benign government policies.

The increase in per capita availability of rice and decline in the cost of production per tone of output contributed to a decline in the real price of rice in international and domestic markets. The unit cost of production is about 20 to 30 per cent lower for high-yielding varieties than for traditional varieties of rice (Yap, 1991), and the cost of rice is 40 per cent lower now than it was in the 1960s. This decline in food prices has definitely benefited the urban poor and landless people in rural areas, who spend more than half their income on food grains.

Rice in the New Millennium

The world's capacity to sustain a favourable balance between food production and population growth has again come under the spotlight, as the global population continues to grow. But this is not the only factor: rice production has suffered a drastic slowdown. During the 1970s and 1980s, it increased at the rate of 2.5-3 per cent per year, but during the 1990s the growth rate was only 1.5 per cent. According to UN estimates, the world population will grow to eight billion by 2025. The bulk of this increase (93 per cent) will occur in developing countries, whose share of the population is projected to increase from 78 per cent in the 1990s to 83 per cent in 2020.

In spite of all the achievements of the green revolution, serious food problems persist. Every 3.6 seconds somebody dies of hunger. Chronic hunger takes the lives of 2400 people every day. Currently there are more than 800 million undernourished people in the developing world, and 300 million children under the age of five die because of hunger and malnutrition, while one out of five babies is born underweight.

According to various estimates, we will have to produce 40 per cent more rice by 2030 to satisfy the growing demand without affecting the resource base in a negative way. This boost in demand will have to be met from less land, with less water, less labour and fewer chemicals. If we

are not able to produce more rice from the land available, land-hungry farmers will destroy forests and move into more fragile terrains such as hillsides and wetlands, with disastrous consequences for biodiversity and watersheds. To meet the challenge of producing more rice from suitable lands, we need rice varieties with higher yield potential and greater yield stability.

Increasing the Yield Potential

Various strategies for increasing the yield potential of rice include conventional hybridization and selection procedures, ideotype breeding, heterosis breeding, wide hybridization and genetic engineering. We will examine each below.

Conventional hybridization and selection procedures

The time-tested strategy for selecting crop cultivars with higher yield potential is conventional hybridization and selection. There are two stages to the process. The first involves the creation of variability through hybridization between diverse parents. In the second, desirable individual plants are selected based on field observations and yield trials. It has been estimated that on average, an increase of about 1.0 per cent has occurred per year in the yield potential of rice over a 35-year period since the development of the first improved variety of rice, IR8 (Peng *et al.*, 2000). Where there is enough investment in research, yields of crops have continuously increased, and there is no reason why further boosts in yield cannot be attained.

Ideotype breeding

Ideotype breeding, which aims to modify the plant's architecture, is another traditional strategy to achieve increases in yield potential. For example, selection for shorter-statured strains of cereals such as wheat, rice and sorghum resulted in a doubling of yield potential. Yield potential is determined by the total dry matter or biomass and the harvest index (HI). Tall and traditional rices had an HI of around 0.3 and a total biomass

of about 12 tonnes per hectare. Thus, their maximum yield was 4 tonnes per hectare. Their biomass could not be increased by an application of nitrogenous fertilizers, as the plants grew excessively tall, tended to lodge or fall over, and produced a decreased instead of increased yield. To increase the yield potential of tropical rice, it was necessary to improve the harvest index and nitrogen responsiveness by increasing the lodging resistance. This was accomplished by reducing the plant height through the incorporation of a recessive gene *sd1* for short stature.

The first short variety, IR8, developed at the International Rice Research Institute (IRRI) also combined other desirable traits such as profuse tillering (sprouting from the base), dark green and erect leaves for good canopy architecture, and sturdy stems. It responded to nitrogenous fertilizer much better and had a higher biomass (about 18 tonnes) and an HI of 0.45. Its yield potential was 8-9 tonnes per hectare (Chandler, 1969).

To increase the yield potential of rice further, a new plant type was conceptualized in 1988 at IRRI. Modern semi-dwarf rices produce a large number of unproductive tillers and excessive leaf area that cause mutual shading, and reduce canopy photosynthesis and sink size, especially when they are grown under direct sowing conditions. To increase the yield potential of these semi-dwarf varieties, IRRI scientists proposed further modifications of plant architecture with the following characteristics:

- Low tillering (9-10 tillers for transplanted conditions).
- No unproductive tillers.
- 200-250 grains per panicle.
- Dark green, thick and erect leaves.
- Vigorous, deep root system.

This proposed ideotype became the "new plant type" (NPT) highlighted in IRRI's strategic plan (IRRI, 1989), and breeding efforts to develop NPT were initiated in 1990. The objective was to develop improved germplasm with 15-20 per cent higher yield than the existing high-yield varieties. Numerous breeding lines with the desired ideotype were developed (Khush, 1995) and shared with the national rice improvement programmes. Three NPT lines have been released in China and two in Indonesia. Other NARS are evaluating and further improving NPT lines.

Heterosis breeding

Yield improvement in maize has been associated with hybrid development. Yields of maize in the US were basically unchanged from the mi-19th century until 1930, and accelerated only after the introduction of commercial 'double cross' hybrids. The subsequent replacement of double cross hybrids by single cross hybrids in 1960 boosted maize yields for the second time. The average yield advantage of hybrids versus cultivars is approximately 15 per cent.

Rice hybrids with a yield advantage of about 10-15 per cent over the best inbred varieties were introduced into China in the mid-1970s and are now planted on about 45 per cent of the land given to rice planting there. Rice hybrids adapted to the tropics have now been bred at IRRI and by NARS and show similar yield advantage. The increased yield advantage of tropical rice hybrids is due to an increase in biomass, higher spikelet number and, to some extent, a higher grain weight. If hybrids are used more in the tropics, the shift should contribute to increased productivity.

Wide hybridization

A crop's gene pool is widened through the hybridization of crop cultivars with wild species, weedy races as well as intra-subspecific crosses. Such gene pools can be exploited to improve many traits, including yield. For example, P.L. Lawrence and K.J. Frey (1976) reported that a quarter of lines from BC_2-BC_4 segregants (that is, plants that differ from either of their parents) from the *Avena sativa* x *Avena sterilis* crosses were significantly higher in grain yield than the cultivated recurrent parent. Nine lines from this study, when tested over years and sites, had agronomic traits similar to the recurrent parent and a 10-29 per cent higher grain yield. The higher yield potential of these inter-specific derivatives was attributed to higher vegetative growth rates or early seedling vigour.

One study (Xiao et al., 1996) reported that some backcross derivates from a cross between an *Oryza rufipogon* accession from Malaysia and cultivated rice outyielded the recurrent parent by as much as 18 per cent. They identified two QTL from wild species with major contribution to yield increase. These QTL are now being transferred to several modern semi-dwarf varieties.

Genetic engineering

The protocols for transforming rice genetically are now so well established it is possible to introduce single alien genes that can selectively modify processes that determine yield. In several crop species, the incorporation of the 'stay green' trait which slows the ageing process in leaves has been a major achievement of breeders in the past decade (Evans, 1993). In some genotypes with this trait, the degradation of the Rubisco protein, which is a decay process in plants, is slower, resulting in longer canopy photosynthesis and higher yields.

In one such engineering feat, the ipt gene from *agrobacterium tumefacions* (Akiyoshi *et al.*,1984) was fused with the sensecence-specific promoter SAG 12 (Gan and Amasino, 1996) and introduced into tobacco plants. Ageing in the leaves and flowers of the transgenic plant was markedly delayed while biomass and seed yield was increased, but other aspects of plant growth and development were normal.

Breeding for Durable Resistance

With modern rice varieties, the full yield potential is not always realized because of the toll taken by attacks from disease and insect organisms. It is estimated that diseases and insects cause losses in yield of up to 25 per cent a year. Genetic improvement to incorporate durable resistance to pests is the preferred strategy to minimize these losses. There is no cost to farmers and resistant cultivars are easily adopted and disseminated, unlike 'knowledge based' technologies. Also, concern for the environment has become an important public policy issue and pest management methods that minimize the use of crop protection chemicals are increasingly finding favour.

Many sources of resistance to major diseases and insects have now been identified, and rice varieties with multiple resistance to diseases and insects have been developed. However, no sources of resistance to sheath blight have been discovered and there are few donors conferring resistance to virus diseases and stem borer. Recent breakthroughs in cellular and molecular biology have provided tools to develop more durably resistant cultivars, and overcome this problem of a lack of donors.

Wide hybridization for disease and insect resistance

Wild species of rice are a rich source of genes for resistance breeding. For example, while no variety of cultivated rice has been found to be resistant to the grassy stunt virus, *Oryza nivara*, a wild species closely related to cultivated rice, is. Its dominant gene for resistance has been transferred to improved germplasm through backcrossing, and incorporated into many widely grown varieties.

When genes are to be transferred from more distantly related species, special techniques such as embryo rescue are employed to reproduce inter-specific hybrids. Jena and Khush (1990) transferred genes for resistance to three biotypes of brown plant hopper from *O. officinalis* to an elite breeding line. In another study (Multani et al.,1994), genes for resistance to the brown plant hopper were transferred from *O. australiensis* to cultivated rice. Similarly, genes for resistance to blast and bacterial blight have been transferred from *O. minuta* to improved rice germplasm.

Molecular marker assisted breeding

Numerous genes for disease and insect resistance are repeatedly transferred from one varietal background to the other. Most genes behave in a dominant or recessive manner and transferring them demands considerable time and effort. Sometimes the screening procedures are cumbersome and expensive and require large field space. If such genes can be tagged with molecular markers, time and money can be saved in transferring them from one varietal background to another as their presence or absence can then be tracked. A molecular marker very closely linked to the target gene and acting as a tag means it can help in indirectly selecting that gene (Jena et al., 2003).

Two of the most serious and widespread diseases in rice production are rice blast, caused by the fungus *Pyrcularia oryzae*, and bacterial blight caused by *Xanthomonas oryzae pv.oryzae*.

The development of durable resistance to these diseases is the focus of a coordinated effort at IRRI using molecular marker technology. Efforts to detect markers closely linked to bacterial blight resistance genes have taken advantage of the availability of near isogenic lines having single genes for resistance. Segregating populations were used to confirm co-segregation between RFLP markers and genes for resistance. Protocols for converting

RFLP markers into PCR based markers and using the PCR markers in marker-aided selection have been established. The PCR markers were also used for pyramiding genes for resistance to bacterial blight. So *xa4, x5, xa13, and Xa21* were combined into the same breeding line (Huang *et al.*, 1997). The pyramided lines showed a wider spectrum and higher level of resistance than lines having only a single gene for resistance. MAS has also been used to move genes from pyramided lines into new plant types as well as into improved varieties grown in India.

Genetic engineering

Protocols for rice transformation have been developed that allow the transfer of foreign genes from diverse biological systems into rice. Direct DNA transfer methods such as protoplast-based techniques and 'gene guns' as well as *Agrobacterium*-mediated procedures are being used for rice transformation. The major targets for rice improvement through transformation are disease and insect resistance.

As early as 1987, genes encoding for toxins from *Bacillus thuringiensis* (Bt) were transferred to tomato, tobacco and potato plants, where they provided protection against lepidopteran insect pests. A major target for Bt deployment in transgenic rice is the yellow stem borer, which is widespread in Asia and causes substantial crop losses. Improved rice cultivars are either susceptible to the insect or have only partial resistance, so engineering them to contain Bt genes is important in Asian regions. And in fact, specially optimized Bt genes have been introduced into rice and show excellent levels of resistance in the laboratory and greenhouse (Datta *et al.*, 1997). Bt rices have also been tested under field conditions in China and have been found to have excellent resistance to diverse populations of yellow stem borer.

Besides Bt genes, other genes for insect resistance — such as those for proteinase inhibitors, *a*-amylase inhibitors and lectins — are also beginning to receive attention. Insects use diverse proteolytic or hydrolytic enzymes in their gut to help in digesting proteins and other food components. Plant-derived proteinase inhibitors or α-amylase inhibitors are of particular interest because these are a part of the natural plant defense system against insect predation. It has been reported (Xu et al., 1996) that transgenic

rice carrying the cowpea trypsin inhibitor (*Cpti*) gene shows enhanced resistance against striped stem borer and pink stem borer.

Several viral diseases cause serious yield losses in rice. A highly successful strategy known as coat protein (CP) mediated protection has been employed against certain of them, such as the tobacco mosaic virus in tobacco and tomato. A coat protein gene from the rice strip virus was introduced into two japonica varieties by electroporation of protoplasts (Hayakawa et al., 1992). The resultant transgenic plants expressed CP at a high level, and exhibited a significant degree of resistance to viral infection; resistance was also inherited to its progeny.

Breeding for Abiotic Stress Tolerance

A series of abiotic stresses such as drought, excess water, mineral deficiencies and toxicities in soil, and unfavourable temperatures affect rice productivity. The progress in developing crop cultivars for tolerance to abiotic stresses has been slow because of a lack of knowledge of tolerance mechanisms, a poor understanding of how resistance or tolerance are inherited, low heritability and a dearth of efficient techniques for screening the germplasm and breeding materials. Nevertheless, rice cultivars with varying degrees of tolerance to abiotic stresses have been developed.

Rainfed rice is planted on about 40 million hectares of land worldwide, and vast areas suffer from drought at some stage of the growth cycle. QTL for various component traits of drought tolerance have been mapped and the information is being utilized to develop improved cultivars with drought tolerance.

Genetic engineering holds great promise for developing rice with drought tolerance. In one study (Garg et al., 2002) *ots A* and *ots B* genes for trehalose biosynthesis were introduced from *Escherichia coli* into rice, and the transgenic rices accumulated trehalose at 3-10 times that of nontransgenic controls. (Trehalose stabilizes biological structures under abiotic stresses.) More, it was found that the transgenic rice had better tolerance of both drought and salinity.

Beyond trehalose, the accumulation of sugar alcohols is a widespread response in plants to environmental stresses that may protect them through osmoregulation, or the maintenance of a balance between water and

dissolved materials. Mannitol, for instance, is a sugar alcohol commonly found in plants. Tobacco plants lacking it were transformed with a bacterial gene *mtlD* encoding mannitol (Tarczynski et al., 1992). In the leaves and roots of some of the engineered plants, mannitol concentrations exceeded 6μ mol/g (fresh weight), whereas it was not detected in these organs in control tobacco plants. Plants grown from the mannitol-containing lines and controls, both in the absence and presence of sodium chloride (NACL) in a culture solution, were then analyzed. The mannitol-containing plants had a better tolerance of salinity (Tarczynski et al., 1993). After 30 days of exposure in the culture solution, the transformed plants increased in height by a mean of 80 per cent, whereas control plants increased by a mean of only 22 per cent over the same interval. It is an approach that is worth trying in rice.

In some areas, rice crops suffer from the effect of floods if submerged for up to 10 days. A few rice cultivars have been identified that survive submergence for 8-10 days, however. Using FR13A, one of the submergence tolerant donors, improved rice cultivars with submergence tolerance have been developed (MacKill et al., 1993).

Conclusion

For over half the world, rice is the key food crop and primary source of calories. More than 92 per cent of the world's rice is grown and consumed in Asia, where 60 per cent of the global population live. Rice accounts for 35 per cent to 75 per cent of the calories consumed by more than 3 billion Asians, and rice consumption is growing in most African and Latin American countries.

So far, production has been able to keep up with consumption. Between 1966 and 2000, the population of densely populated low-income countries grew by 90 per cent, but rice production increased by 130 per cent between 1966 and 2000. And that year, the average in food availability per person was 18 per cent higher than in 1966. This dramatic achievement in world food production was possible because of technological advance — the development of high-yielding, disease and insect-resistant varieties of rice.

This happy situation may not last without another boost in production. The demand for rice is now increasing at the rate of 1.5 per cent per year and according to various estimates, the world's farmers will have to produce 40 per cent more rice by 2030. To meet this challenge, rice varieties with higher yield potential and greater yield stability are needed. Various strategies for increasing the yield potential of rice include techniques from conventional hybridization and selection procedures all the way through to genetic engineering. To increase yield stability, genes for resistance to biotic and abiotic stresses are being incorporated through conventional and genetic engineering approaches.

References

1. Akiyoshi, D. E. et al., 1984. T-DNA Agrobacterum tumefaciens encodes an enzyme for cytokinin biosynthesis. Proceedings of the National Academy of Sciences. Vol. 81, p 5994
2. Chandler, R.F.1969. Plant morphology and stand geometry in relation to nitrogen. In Physiological aspects of crop yield. Eastin, J. D. et al., (eds). ASA Publication, Madison, Wisconsin, pp 265-285.
3. Datta, S. K. et al., 1997. Production and molecular evaluation of transgenic rice plants. IRRI Discussion Paper Series No. 21. International Rice Research Institute, Manila, Philippines
4. Evans, L. T. 1993. Raising the ceiling to yield: key role of synergism between agronomy and plant breeding. In new frontiers in rice research. Muralidharan, K. and Siddiq, E.A. (eds). Directorate of Rice Research, Hyderabad, India, pp 103-107
5. Gan, S. and Amasino, R.A..1996. Inhibition of leaf senescence by autoreglated production of cytokinin. Science. Vol. 270, pp 1986-1988
6. Garg, A. K. et al., 2002. Trehalose accumulation in rice plants confers high tolerance levels to different abiotic stresses. Proceedings of the National Academy of Sciences. Vol. 99, pp 15898-15903
7. Hayakawa, T., Zhu, Y., Ito, K., and Kimura, Y. 1992. Genetically engineered rice resistant to rice stripe virus, an insect transmitted virus. Proceedings of the National Academy of Sciences. Vol. 89, pp 9865-9869
8. Huang, N., et al., 1997. Pyramiding of bacterial blight resistance genes in rice: marker assisted selection using RFLP and PCR. Theoretical and Applied Genetics. Vol. 95, pp 313-320
9. IRRI. 1989. IRRI towards 2000 and beyond. International Rice Research Institute, Manila, Philippines

10. Jena, K.K., Moon, H. P. and Mackill, D. J. 2003. Marker assisted selection — a new paradigm in plant breeding. Korean Journal of Breeding. Vol. 35, No. 3, pp 133-140
11. Khush, G. S. 1995. Breaking the yield barrier of rice. Geo Journal. Vol. 35, pp 329-332
12. Lawrence, P. L., and Frey, K. J. 1976. Backcross variability for grain yield in species crosses (Avena Sativa L x A. sterilis L.). Euphytica. Vol. 24, pp 77-85
13. MacKill, D. J., et al., 1993. Improved semi-dwarf rice lines with tolerance to submergence. Crop Science. Vol. 33, pp 749-753
14. Multani, D. S. et al.,1994. Development of monosomic alien addition lines and introgressions of genes from Oryza australiensis Domin to cultivated rice, O. Sativa. Theoretical and Applied Genetics. Vol. 88, pp 102-109
15. Peng, S. R. C. et al., 2000. Grain yield of rice cultivars and lines developed in the Philippines since 1966. Crop Science. Vol. 40, pp 307-314
16. Tarczynski, M.C. Jensen, R. G. and Bohnert, H. J. 1992. Expression of a bacterial mtl D gene in transgenic tobacco leads to production and accumulation of Mannitol. Proceedings of the National Academy of Sciences. Vol. 89, pp 2600-2604
17. Tarczynski, M.C. Jensen, R. G. and Bohnert, H. J. 1993. Stress protection of transgenic tobacco by production of osmolyte mannitol. Science. Vol. 259, pp 508-510
18. Xiao, J., S. Grandillo, S. N. Ahn, S. R. McCouch and S. D. Tanksley 1996. Genes from wild rice improve yield. Nature 384-1223-224
19. Xu, D., Q. et al., 1996. Constitutve expression of a cowpea trypsin inhibitor gene cpti in transgenic rice plants confers resistance to two rice insects. Molecular Breeding. Vol. 2, pp167-173
20. Yap, C.L.1991. A comparison of the cost of producing rice in selected countries. Food and Agriculture Organization (FAO) Economic and Social Development Paper No 101. FAO, Rome, Italy

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Biofortification in Brazil: The HarvestPlus Challenge Programme

Marília Nutti, Edson Watanabe, José Luiz de Carvalho and Howarth Bouis

Introduction

Globally, over 840 million people lack enough food to meet their basic daily needs. Far more — an estimated three billion — suffer the insidious effects of micronutrient deficiencies because they do not have the money to buy the amounts of meat, poultry, fish, fruits, legumes and vegetables they need to stay fully nourished. Women and children in sub-Saharan Africa, South and Southeast Asia, and Latin America and the Caribbean are especially at risk of disease, premature death, and impaired cognitive ability because of diets poor in crucial micronutrients, particularly iron, vitamin A, iodine, and zinc (McGuire, 1993).

The World Health Organization has shown, based on micronutrient deficiency data, that this problem is not exclusive to developing countries but can also be observed in the industrialized world. Among the most studied micronutrients, iron, vitamin A and iodine are pointed out as the ones most correlated to public health problems, in Brazil and worldwide. Also, calcium, zinc, selenium and copper, among other essential elements, are extremely important for adequate nutrition and normal development (Kennedy et al., 2003).

Today, most efforts to combat micronutrient malnutrition in the developing world focus on providing vitamin and mineral supplements for pregnant women and young children and on fortifying foods with these nutrients through postharvest processing. And these approaches have accomplished much. In regions with adequate infrastructure and well-established markets for delivering processed foods such as salt, sugar and cereal flours, fortifying food can hugely boost micronutrient intake among vulnerable people.

In Brazil, efforts in this direction started a long time ago, beginning with the manufacture of iodine-fortified salt and water fluoridation in some regions of the country. More recently, it has become mandatory to fortify wheat and maize flours with iron to prevent anaemia and with folic acid so pregnant women can protect the foetus from developing neural tube defects (Cozzolino, 2005).

But there are limits to commercial fortification and supplementation. Fortified foods may not reach a large number of the people most in need because there may be no shops selling them in their area, or adequate transport routes. Supplementation depends on a highly functional health infrastructure, which is all too often lacking in developing countries. So new approaches are needed to complement existing interventions.

The introduction of biofortified crops — varieties bred for increased mineral and vitamin content — will complement existing nutrition interventions and provide a sustainable, low-cost way of reaching people who have poor access to markets or healthcare. Once the investment is made to develop nutritionally improved varieties at central research locations, seeds can be adapted to growing conditions in numerous countries. Biofortified varieties have the potential to provide ongoing benefits year after year throughout the developing world at a lower cost than either supplementation or fortification during processing.

The HarvestPlus Challenge Program on Biofortification was developed with the objective of improving the nutritional quality of the main food crops, adapted to the regions where they are grown. Its goal is to ensure that scientific and technological advances improve the diet of the poorest populations in the world — subsistence farmers living in the marginal zones of the tropics.

Micronutrient Deficiency and Biofortification

Diets deficient in iron and zinc can cause anaemia, a reduction in capacity to work, immune problems and retarded growth, and can even be fatal (WHO, 2000). Iron deficient anemia is probably the biggest nutritional problem in Brazil, affecting from 30 per cent to 80 per cent of under-fives. The deficiency occurs across the board — independently of social class or geographic distribution. The most important sources of iron in Brazil are common beans and red meat, and the absorption potential for this mineral is around 1-7 per cent (Favaro, 1997).

Zinc deficiency is not studied as much as iron deficiency, but since the food sources for these two nutrients are the same, the incidence of zinc deficiency will also be very high. Zinc is required for the activity of more than 300 enzymes, acting on the immune system and gene expression, among other functions (McCall, 2000). Little is known about zinc deficiency in developing countries, but foods rich in bioavailable iron are usually also rich in bioavailable zinc.

Vitamin A is essential for vision, growth and protection against diseases. Deficiency is a serious health problem in developing countries, and causes blindness in children in 80 countries around the world. Increasing intake of pro-vitamin A or carotenoids is one of the recognized ways to combat deficiency (Cozzolino, 2005).

Deficiencies in these micronutrients are obviously often caused by simply not having enough to eat. But levels of iron, zinc and vitamin A in foods can also vary, given a number of factors:

- Plant characteristics such as age, degree of maturation, species, variety, cultivar and diet.
- Environmental characteristics such as climate, soil, rain, season.
- Processing parameters such as storage, temperature, preservation method and preparation (Welch, 2001).

In developing countries, food fortification with vitamin A and iron, as well as the distribution of supplements with these micronutrients to target populations, are the most common approaches to fighting hipovitaminosis A and iron deficiency anaemia (FAO/WHO, 1993).

But biofortification, which is backed by sound science, has been shown to be highly useful in this context. Preliminary research examining the feasibility of a plant breeding approach for improving the micronutrient content of staple crops has found that substantial, useful genetic variation exists in key crops. The research has also shown that breeding programs can readily manage traits governing nutritional quality, which in some crops are highly heritable and simple to screen for; that desired traits are sufficiently stable across a wide range of growing environments; and that traits for high nutrient content can be combined with superior agronomic characteristics and a capability for high yields.

The HarvestPlus Program

This is where the HarvestPlus Challenge Program on Biofortification comes in. HarvestPlus is an initiative of the Consultative Group on International Agricultural Research (CGIAR), which involves the collaborating CGIAR research centres (the International Centre for Tropical Agriculture – CIAT, the International Maize and Wheat Improvement Centre – CIMMYT, the International Potato Centre – CIP, the International Centre for Agricultural Research in the Dry Areas – ICARDA, the International Crops Research Institute for the Semi-Arid Tropics – ICRISAT, the International Food Policy Research Institute – IFPRI, the International Institute of Tropical Agriculture – IITA, and the International Rice Research Institute – IRRI) and partner institutions. These include national agricultural research systems in developing countries; various universities as well as academic departments of human nutrition in developing and developed countries; non-governmental organizations; the Plant, Soil, and Nutrition Laboratory; and the US Department of Agriculture, including its Agricultural Research Service (USDA/ARS) and the Children's Nutrition Research Centre, Baylor College of Medicine (USDA/ARS).

CIAT and IFPRI are coordinating activities to do with plant breeding, human nutrition, crop dissemination, policy analysis and impact that will be carried out at international agricultural research centres, national agricultural research and extension institutions, and departments of plant science and human nutrition at universities round the world. NGOs in

Objectives of HarvestPlus: Year 1 to 10

Period of Decade	Objectives
Year 1 to 4	Determine nutritionally optimal breeding objectives; screen CGIAR germplasm for high iron, zinc, and beta-carotene levels. Initiate crosses of high-yielding adapted germplasm for selected crops; document cultural and food-processing practices, and determine their effect on micronutrient content and bioavailability; discern the genetics of high micronutrient levels, and identify the markers available to facilitate the transfer or traits through conventional and novel breeding strategies; carry out in vitro and animal studies to determine the bioavailability of the enhanced micronutrients in promising lines; begin bioefficacy studies to determine the biological effect of biofortified crops on the micronutrient status of humans; initiate studies to identify the trends — and factors driving these trends — in the quality of the diets of poor people; conduct benefit-cost analyses of plant breeding and of other food-based interventions to control micronutrient malnutrition.
Year 5 to 7	Continue bioefficacy studies; initiate participatory plant breeding; adapt high-yielding, conventionally bred, micronutrient-dense lines to select regions; release new conventionally bred biofortified varieties to farmers; identify gene systems with potential for increasing nutritional value beyond traditional breeding methods; produce transgenic lines at experimental level and screen for micronutrients. Test for compliance with biosafety regulations; develop and implement a marketing strategy to promote the improved varieties; begin production and distribution.
Year 8 to 10	Scale up the production and distribution of the improved varieties; determine the nutritional effectiveness of the program, and identify factors affecting the adoption of biofortified crops, the impact on households' resources, and the effects on the health of individuals.

developed and developing countries, farmers' organizations, and public-private sector partnerships will strengthen the alliance and provide links to consumers.

The initial biofortification efforts will focus on six staple crops, for which feasibility studies have been completed: beans, cassava, maize, rice, sweet potatoes and wheat. The programme will also examine the potential to nutritionally enhance 10 additional crops that are important in the diets of people with micronutrient deficiencies: bananas/plantains, barley, cowpeas, groundnuts, lentils, millet, pigeon peas, potatoes, sorghum and yams.

HarvestPlus was planned for a 10-year period and is funded by the Bill and Melinda Gates Foundation, the UK Department for International Development (DFID), the Danish International Development Assistance

(DANIDA), Swedish International Development Assistance (SIDA), the United States Agency for International Development (USAID), the World Bank, the Asian Development Bank (ABD) and the Canadian International Development Agency (CIDA).

HarvestPlus Activities in Brazil

In Brazil, HarvestPlus is coordinated by the Brazilian Agricultural Research Corporation agency (Embrapa), which includes a number of centres that are currently part of the research network: Embrapa Food Technology, Embrapa Rice and Beans, Embrapa Cassava and Tropical Fruits, Embrapa Maize and Sorghum, Embrapa Genetic Resources and Biotechnology, Embrapa Mid-North and the State University of Campinas's food science department. The inclusion of Embrapa Soils to carry out research on the composition of micronutrients of Brazilian soils has been proposed.

The programme focuses on crops that are already widely produced and consumed in Brazil, so farmers and consumers will not have to change their diet to benefit from biofortification. Moreover, breeding to improve the mineral content will not necessarily alter the appearance, taste, texture or cooking qualities of the food made from the crop — all important factors for consumers.

The crops are also likely to be attractive to farmers, as they combine high micronutrient content with high yield, and market success of nutritionally improved varieties is virtually guaranteed. In fact, research showing that high levels of minerals in seeds also aid plant nutrition has fueled expectations of boosted productivity in biofortified strains.

One way to ensure that farmers will like the new varieties is to give them a say in what traits are bred into the plants. Participatory plant breeding, in which scientists take farmers' perspectives and preferences into account during the breeding process, can be more cost-effective than confining breeding to research stations.

So far, the programme has collaborated with 10 African countries to develop local capacity for carotenoid analysis; a hands-on training course on carotenoid detection and analysis was organized in Tanzania in July 2005. Earlier that year, the Brazilian HarvestPlus team of plant breeders and nutritionists presented the proposed work to an audience of Brazilian

policymakers and scientists — a group critical for paving the programme's way generally, and enabling biofortification to become a viable strategy for reducing micronutrient malnutrition. Currently, the team is also working on the screening of germplasms of cowpeas, wheat and sweet potato.

Conclusion

A common problem in many developing countries is the lack of delivery systems to get products, be they health or agronomic inputs, to the poorest people. HarvestPlus is overcoming this constraint via the seed-based technologies inherent in the biofortification approach. When households grow micronutrient-rich crops, the delivery system for micronutrients is built into the existing food production and marketing process. Little intervention or investment is needed once farmers have adopted the new seed. Moreover, saving and sharing the seed is easy for even the poorest households.

Embrapa has valuable experience in the development and promotion of local systems of seed distribution because of its ongoing work with seed systems and its contributions to disaster response. These established systems offer a natural route for disseminating biofortified seed. Local agricultural committees and small-farmers seed enterprises in particular will play a crucial role in getting micronutrient-rich varieties into the hands of growers.

During the first year of the project, around 3000 varieties of cassava, beans and maize were selected and multiplied. Soon evaluations of the levels of iron, zinc, total carotenoids and beta-carotene will be in place. Breeders will then work on the promising varieties using participatory traditional plant breeding in order to develop biofortified varieties. To estimate nutrient loss (beta-carotene in cassava, and iron and zinc in beans) during processing and storage, retention studies using conventional varieties will also be carried out during the first year of the project. A target of the project is that countries of Latin America, the Caribbean, Africa and Southeast Asia will be integrated into it, with Brazil developing and transferring not only the biofortified varieties, but also post-harvest technology for these crops.

The ultimate solution to eradicating poor nutrition in developing countries is to substantially increase the consumption of meat, poultry, fish, fruits, legumes and vegetables among the poor. Achieving this will take many decades and untold billions of dollars. Meanwhile, biofortification makes sense as part of an integrated food-systems approach to address the problem of nutrition among the poor. It goes straight at the root causes of micronutrient malnutrition, targets the poorest people, uses built-in delivery mechanisms, is scientifically feasible and cost-effective, and complements other ongoing interventions to control micronutrient deficiencies. In short, it is an essential first step in enabling rural households to improve family nutrition and health in a sustainable way.

References

1. Cozzolino, S. M. F. 2005. Biodisponibilidade de Nutrientes. Manole, Barueri, Brazil.
2. Favaro, D.I.T. 1997. Determination of various nutrients and toxic elements in different Brazilian regional diets by neutron activation analysis. The Journal of Trace Elements in Medicine and Biology. Vol. 11, pp 129-136.
3. Kennedy, G., Nantel, G., Shetty, P. The scourge of "hidden hunger": global dimensions of micronutrient deficiencies. Food Nutr. Agr. Vol. 32, No. 8, pp 8-16
4. McCall, K.A. et al., 2000. Function and mechanism of zinc metalloenzymes. Journal of Nutrition. Vol.130, pp1437S-1446S.
5. McGuire, J. 1993. Addressing micronutrient malnutrition. SCN News, Vol. 9, pp 1-10.
6. Welch, R.M., 2001. Micronutrients, agriculture and nutrition: linkages for improved health and well being. In: Perspectives on the Micronutrient Nutrition of Crops, edited by K. Singh, S. Mori and R.M. Welch. Scientific Publishers, Jodhpur, India. pp 237-289.
7. WHO. 2000. Global database on anemia and iron deficiency. Available at: http://www.who.int/nut/db-mdis

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BIOTECHNOLOGY TO RELIEVE THE EFFECTS OF DROUGHT

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Harnessing New Science to Meet the Challenges of Drought

Magdy Madkour

Introduction

The International Centre for Agricultural Research in the Dry Areas (ICARDA) is one of the 15 centres strategically located all over the world and supported by the Consultative Group on International Agricultural Research (CGIAR). ICARDA works through a network of partnerships with national, regional and international institutions, universities, non-governmental organizations and ministries in the developing world; and with advanced research institutes in industrialized countries.

ICARDA's mission is to improve the welfare of people through research and training in dry areas of the developing world, by increasing the production, productivity and nutritional quality of food, while preserving and enhancing the natural resource base. The environment in dry areas is harsh, stressful and variable, and agriculture in these areas faces more complex challenges than in areas with adequate rainfall. ICARDA is committed to the advancement of agricultural research; free exchange of germplasm and information for research; protection of intellectual property rights, including indigenous knowledge of farmers; human resources development; the sustainable use of natural resources, and poverty alleviation, particularly among women and children. ICARDA

serves the entire developing world for the improvement of barley; lentil, and faba bean; and dry-area developing countries for the on-farm management of water, improvement of nutrition and productivity of small ruminants (sheep and goats), and rehabilitation and management of rangelands. In Central and West Asia and North Africa (CWANA), ICARDA is responsible for the improvement of durum and bread wheats, chickpea, pasture and forage legumes; and for the protection and enhancement of the natural resource base of water, land, and biodiversity.

Scarcity of water resources is a serious threat to agriculture in the dry areas, particularly the West Asia and North Africa (WANA) region. The average annual per capita renewable supplies of water in the region is now less than 1500 m^3, much below the world average of about 7000 m^3 (Figure 1). This is expected to fall to less than 700 m^3 by the year 2025. The current water supplies will not be able to support economic growth in the region. Water scarcity is already hampering the development efforts in all countries of the Arabian Peninsula, Egypt, Jordan, Morocco, Palestine, Tunisia and Yemen. Other countries of the region such as Syria, Iraq, Algeria and Lebanon are increasingly affected as scarcity grows year after year.

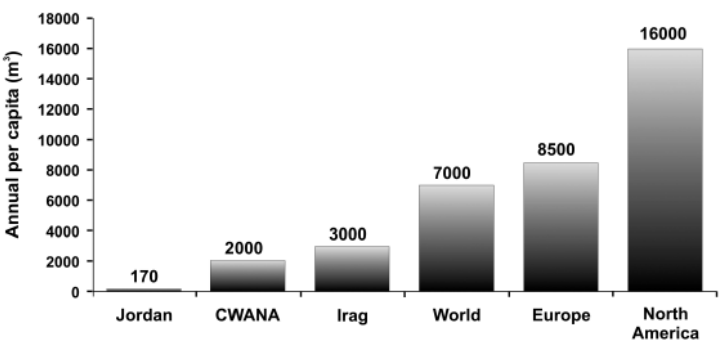

Figure 1. Annual renewable water share

Biotic and abiotic stresses are major limitations to yields of cereal and legume crops in the CWANA region. Drought, salinity and cold stress alone cause nearly 35 per cent of crop losses throughout the world. Climate change will increase the frequency of droughts, particularly in the WANA region.

ICARDA has a world mandate for the improvement of crops to increase their productivity and adaptability, while protecting the natural

resource base, in the dry areas. To achieve this, a number of new tools of science (Figure 2) are harnessed to improve the research efficiency and to meet the challenges of agriculture in the dry areas. Remote sensing and GIS are proving very useful in devising more efficient water-capturing and land management methods. Modeling tools can help in maximizing the water-use efficiency. Expert systems are being increasingly used to support farmers in decision-making. Application of biotechnology have made it possible to develop crop varieties with improved stress resistance and water-use efficiency and thus offer great promise in safeguarding the global future food security.

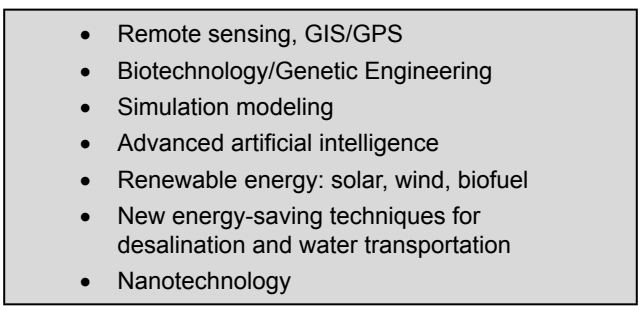

Figure 2. New tools of science to address drought

Biotechnology consists of a gradient of technologies, ranging from the long-established and widely used techniques of traditional biotechnology (for example, food fermentation and biological control), through to novel and continuously evolving techniques of modern biotechnology (Figure 3) (Persley, 1990; Doyle and Persley, 1996).

Over the past two decades, significant increases in advances in modern technology were evident. A number of these scientific techniques is used by ICARDA scientists to develop knowledge-intensive solutions to sustainable agricultural development in countries of the dry areas of the world. The following are examples of the various applications of Biotechnology adopted at ICARDA in its efforts to address the complexity of drought among other biotic and abiotic stresses:

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

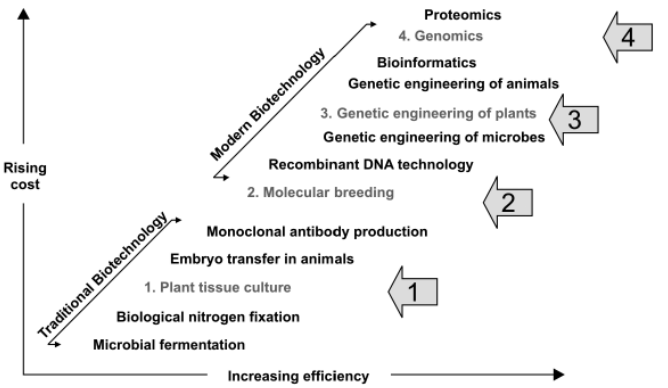

Figure 3. Gradients of Biotechnology

because of the presence of a neurotoxin in the seeds. Recently, existing protocols for explants 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.

Date Palm *(Phoenix dactylifera)*, a second example of plants for dry areas, has adapted in areas characterized by long dry summers and techniques were used to vegetatively propagate date palm to overcome problems associated with the relatively slow sexual propagation through seeds. ICARDA is implementing an ambitious tissue culture-based date palm improvement program that focuses on the production of true-to-type plants either through organogenesis or somatic embryogenesis.

Isolated microspore culture systems as well as interspecific crosses with *H. bulbosum* and maize are being used for the development of double haploid (DH) lines for barley and wheat at ICARDA. DH breeding for the barley program is used to develop mapping populations for drought tolerance. DH breeding for the spring bread wheat program is used specifically to introgress Hessian fly resistance for North Africa and yellow rust resistance into adapted germplasm. DH breeding for the ICARDA facultative and winter wheat program is being used to introgress yellow rust resistance.

Genetic Resources Collections

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 which represents approximately 20 per cent of the germplasm in CGIAR centers. Particularly important are the landraces and wild relatives that have evolved under harsh conditions over millennia. About 70 per cent of our collections are now geo-referenced. This collection-site information combined with climatic layers in GIS 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 partners all over the world. On average, the Centre distributes 35,000 samples per year. Overall, the shift from collection and *ex situ* conservation of plant germplasm to its characterization, evaluation, documentation will help to utilize the biodiversity held at ICARDA.

A number of DNA fingerprinting techniques i.e. 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, such databases also provides 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).

Intra- and inter-specific 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, suggesting that the nuclear genome has evolved differently from the cytoplasmic genome in the genus *Aegilops*.

In order to examine how molecular polymorphism in barley landraces, sampled from 5 different ecogeographical regions of Syria and Jordan, is organized and partitioned, genetic variability at 21 nuclear and 10 chloroplast micro satellite loci was examined (Russell et al., 2003). Chloroplast polymorphism was detected, with most variation being ascribed to differences between the 5 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 5 sites from each of 5 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/ interaction was also detected between the chloroplast and nuclear SSRs together with non-random association (linkage disequilibrium) of alleles at both linked and unlinked SSR loci. These results clearly 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.

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, cold tolerance and others were evaluated at the ICARDA research stations Tel Hadya and Breda during the years 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, specially 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 amplified fragment length polymorphism (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 per cent of the total variation. On 7BL, a major microsatellite (Xgwm344) explained by itself 53 per cent, whereas on 7AL, the other two QTLs have contributed 13 and 6 per cent. 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.

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 single nucleotide polymorphisms (SNPs) in pathogen or abiotic stress resistance genes. We utilize 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 PCR reaction 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.

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 revolution of biotechnology for functional genomics, it allows researchers to screen tens of thousands of genes simultaneously in multiple tissues under a myriad of experimental conditions, which is significantly different from the classical idea of investigating 'one (or a few) gene at a time'.

Considerable complexity has been shown 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-, 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, 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.

Transformation technology

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, faba bean, their efficiency needs to be improved (Table 1). Efficient transformation and regeneration systems are available for cereals such as wheat (Pellegrineschi et al., 2002) and barley (Murray et al., 2004).

The main steps of lentil and chickpea transformation technique have been established at ICARDA by using *Agrobacterium*-mediated transformation to transfer thirteen different constructs into lentil and chickpeas to enhance their resistance to drought, salinity, herbicide, fungi and oxidative stress. Several selectable marker and reporter genes are used in different transformation protocols. Now, our DREBIA gene (in addition to twelve others) is available in our laboratories harbouring in old and new vectors. Twenty-five transformation experiments were conducted using the chickpea line ILC 482 to transfer the DREBIA gene. Recently we established chickpea grafting on untransformed 5 days-old seedlings, germinated on ½ MS medium supplemented with full strength hormone.

Currently rooting experiments are in progress to test the effect of different concentrations of IAA, IBA and BAP on rooting efficiency.

Also, 18 transformation experiments were conducted to transfer the DREBIA gene into three lines of lentil (IL 5588, ILL 5883 and ILC 5582) using two plasmid constructs. Forty-six putative transgenic explants were grafted; 72 per cent of events were survived and transferred to pots. The PCR was carried out to confirm the results with the same information mentioned for chickpea. Twenty-one TO plants were transgenic (approximately one per cent).

ICARDA is acquiring and testing these new technologies in collaboration with advanced research institutes and is making the technology available for the scientist in the National Agricultural Research Systems (NARS) in the region.

Table 1. Genes/phenotype category in chickpea and lentil transformation at ICARDA

Gene Product	Phenotype Category
Phosphinothricin-N-acetyl-transferase (PAT)	Herbicide resistance
Stilbene synthase (vst-1)	Ascochyta blight resistance
Dehydration responsive element (Dreb1A)protein Drought and salinity	Drought and salinity
Gluthathione S-transferase/peroxidase (GST/GPX)	Stress tolerance
Gluthathione S-transferase T2 (GST-T2)	Stress tolerance
Gluthathione S-transferase T3 (GST-T3)	Stress tolerance
Gluthathione S-transferase T5 (GST-T5)	Stress tolerance
Thioredoxin peroxidase (Tpx1	Stress tolerance
Ethylene-Responsive Element Binding Proteins (EREBP)	Drought

References

1. Abd-El-Moneim A., Van Dorrestein B., Baum M et al., (2000). Improving the nutritional quality and yield potential of grasspea (Lathyrus sativus L) Food Nutri. *Bull.* 2000; 21:493-496
2. Baum M, Grando S., Backes G., 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. 2003 Nov; 107(7):1215-25.

3. Chabane, K., Ablett, G.A., Cordeiro, G.M., Valkoun, J., Henry, R.J. (2004). EST versus genomic derived microsatellites for genotyping wild and cultivated barley. Genetic Resources and Crop Evolution, in press.
4. Comai L, Till BJ, SH Reynolds, et al., (2004). Large-scale discovery of natural polymorphisms by Ecotilling. Plant Journal 37:778-786
5. Dale PJ. The GM debate: science or scaremongering? Biologist (London). 2000 Feb; 47(1):7-10. Review.
6. Doyle, J.J. and Persley, G.J. (1996). Enabling Safe Use of Biotechnology: Principles and Practice. Environmentally Sustainable Development Studies and Monographs Series. No. 10, World Bank, Washington. DC.
7. Elouafi I, Nachit MM, Martin LM (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.
8. Eujayl I, Sorrells M. E., Baum M, et al., (2002). Isolation of EST-derived microsatellite markers for genotyping the A and B genomes of wheat. Theor Appl Genet.2002; 104:399–407.
9. Murray F., Brettell R., Matthews P., 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.
10. Pellegrineschi A., Noguera L. M., Skovmand B., et al., (2002). Identification of highly transformable wheat genotypes for mass production of fertile transgenic plants. Genome. 45(2):421-30.
11. Persley, G.J. (1990). Beyond Mendel's Garden: Biotechnology in the Service of World Agriculture. No. 1. CAB International, Wallingford. UK.
12. Russell J. R., Booth A, Fuller JD, 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
13. Sasanuma T., Chabane K., 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.
14. Sasanuma, T., Chabane, K., Endo et al., (2002). Genetic diversity of wheat wild relatives in the Near East detected by AFLP. Euphytica 127(1): 81-93.
15. 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
16. Somers D. D.A. Samac, P. M. Olhoft. Récent Advances in Legume Transformation. Plant Physiol. 131, 2003 892-899.
17. Öztürk Z. N., Talamé V., Deyholos M. et al., (2002) Monitoring Large-Scale Changes in Transcript Abundance in Drought-and Salt-stressed Barley. Plant Molecular Biology 48:551-573.
18. Udupa S. M., Robertson L. D., Weigand F. 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.

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Plants, Genes and Drought Stress

Kazuo Shinozaki and
Kazuko Yamaguchi-Shinozaki

Introduction

Water deficit has adverse effects on plant growth. Therefore, drought stress is the most severe environmental stress for plant growth and crop production. Plants respond and adapt to drought stress in order to survive under water deficit conditions. Drought stress induces various biochemical and physiological responses in plants. Stomata closure decreases water loss form leaves. Plants accumulate various metabolites, such as sugars, sugar alcohols and amino acids, which are thought to function in osmotic adjustment, scavenging reactive oxygen species and so on. Hundred of genes have been identified that respond to drought stress at transcriptional level by microarray (see Shinozaki et al., 2003, Zhang et al., 2004, Bartels and Sunkar 2005). Their gene products are thought to function in stress tolerance and response. Stress-inducible genes have been used to improve stress tolerance of plants by gene transfer. It is important to analyze functions of stress-inducible genes not only for further understanding of molecular mechanisms of stress tolerance and response of higher plants but also for improvement of stress tolerance of crops by gene manipulation (see Bartels and Sunkar 2005, Umezawa et al., 2006a).

Phytohormone, abscisic acid (ABA), is produced under water deficit conditions and plays important roles in response and tolerance against dehydration. ABA functions in stomata closure in leaves and stress-inducible gene expression. It appears that dehydration triggers the production of ABA, which, in turn, induces various genes. It has been described the existence of ABA-independent as well as ABA-dependent signal-transduction cascades between the initial signal of drought stress and the expression of plant genes. Cis- and trans-acting elements that function in ABA-independent and ABA-dependent gene expression by drought stress have been precisely analyzed. A variety of transcription factors have been shown to function in stress-responsive gene expression, which suggests a complex regulatory mechanism in responses to drought stress (see Shinozaki et al., 2003, Yamaguchi-Shinozaki and Shinozaki 2006).

Complex molecular mechanisms are involved in gene expression and signal transduction in response to drought stress. Details of molecular mechanisms of regulating plant genes to drought stress still remain to be solved concerning signal transduction cascades. Genetic and molecular approaches have been performed to solve complex abiotic stress signal transduction pathways (see Zhang et al., 2004). In this Biovision 2006 proceeding article, functions of drought-inducible genes, regulation of their gene expression and signal-transduction pathways in drought stress response and tolerance are discussed mainly based on our recent studies (see Yamaguchi-Shinozaki and Shinozaki 2006, Umezawa et al., 2006a). Molecular approaches to improve drought stress tolerance by gene transfer of stress-inducible genes are described, which is important for molecular breeding of drought stress tolerance.

Isolation of Drought-inducible Genes

Many plant genes are induced by environmental stresses, such as drought, low temperature and high salinity. These stress-inducible genes have been cloned using various methods, such as differential cloning, differential display, and so on. Using PCR, many drought-inducible genes have been identified to encode proteins involved in transcription, signal

transduction and other regulatory processes. Using yeast transformation, plant genes that are involved in osmotic or high salinity stress tolerance have been cloned (see Shinozaki et al., 2003, Umezawa et al., 2006a).

Recently, many stress-inducible genes have been identified using micorarray. Microarray technology has been developed extensively and now has become a powerful tool for global analysis of expression profiles of genes in response to various abiotic and biotic stresses and various treatments with hormones and chemicals. Expression profiles of genes under drought, cold and high-salinity stress conditions are analyzed using micorarray and GenChip (see Shinozaki et al., 2003, Yamaguchi-Shinozaki and Shinozaki 2006). Various kinds of transcripts have been reported to be increased after drought, cold and high-salinity treatments. Many drought-inducible genes are also induced by salt stress and low temperature, which suggests the existence of similar mechanisms of stress responses (Shinozaki et al., 2003). More significant crosstalk is observed between drought and high salinity responses than that between drought and cold responses.

Function of Drought-inducible Genes

Various genes respond to drought-stress, and functions of their gene products have been analyzed using various mutants and transgenic plants. Genes induced during drought-stress conditions are thought to function not only in protecting cells from water deficit by the production of important metabolic proteins but also in the regulation of genes for signal transduction in drought stress response (Bartels and Sunkar 2005, Umezawa et al., 2006a). Thus, these gene products are classified into two groups. The first group includes proteins that probably function in stress tolerance; such as chaperones, LEA (Late Embryogenesis Abundant) proteins, osmotin, antifreeze proteins, mRNA binding proteins, key enzymes for osmolytes biosynthesis, water channel proteins, sugar and proline transporters, detoxyfication enzymes and various proteases. LEA proteins, chaperones and mRNA binding proteins have been analyzed biochemically and shown to be involved in protecting cells from dehydration. Proline, glycine betaine and sugars function as osmolytes and reactive oxygen species (ROS) in

protecting cells from dehydration. Key enzymes of several osmolytes have been cloned and analyzed biochemically. Water channel proteins, and various types of transporters are thought to function in transport of water and small metabolites, respectively, through plasma membranes and tonoplast under stress conditions. Detoxification enzymes are involved in protection of cells from ROS. Proteases and nucleases are thought to be required for protein turnover and recycle of amino acids and nucleotides.

The second group of drought-inducible genes contains protein factors involved in further regulation of signal transduction and gene expression, such as protein kinases, transcription factors and enzymes in phospholipids metabolism and ABA metabolism involved in stress response (Bartels and Sunkar 2005, Umezawa et al., 2006a). Genes for a variety of transcription factors that contain typical DNA binding motifs have been demonstrated to be stress-inducible. These transcription factors function in further regulation of various functional genes under stress conditions. Various protein kinase genes are unregulated by dehydration. Stress-inducible genes for protein phosphatases are also reported. These protein kinases and phosphatases may be involved in modification of functional proteins and regulatory proteins involved in stress signal transduction pathways. Phospholipids, such as inositol 1,4,5-triphosphate, diacylglycerol and phospahtidic acid, are shown to be involved in stress signaling. Enzymes involved in phospholipids metabolism of which genes are stress-inducible may play important roles in stress signaling as well. Enzymes involved in ABA biosynthesis and metabolism are important in the regulation of the level of ABA during dehydration and rehydration. Existence of variety of drought-inducible genes suggests complex responses of plants to drought stress.

Regulation of Drought-inducible Gene Expression

ABA is *de novo* synthesized in response to mainly drought and high salinity stress. Recently, genes involved in ABA biosynthesis and catabolism have been identified based on genetic and genomics analysis (Nambara and Marion-Poll, 2005, Umezawa et al., 2006b).

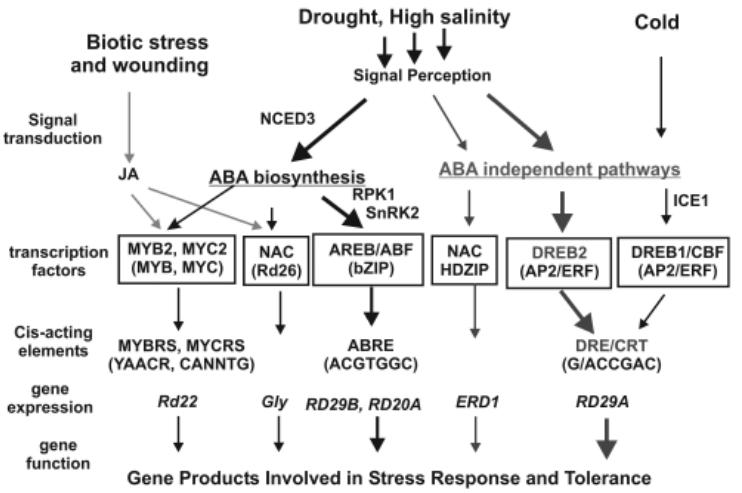

Figure 1. Gene products involved in stress responses and tolerance

Several genes involved in ABA biosynthesis are induced by drought and high salinity. This indicates important roles of ABA in drought and salinity stress responses. ABRE is a major cis-acting element in ABA-responsive gene expression. Two ABRE motifs are important cis-acting elements in ABA-responsive expression of Arabidopsis *RD29B* gene (Uno et al., 2000). Basic leucine zipper (bZIP) transcription factors, AREB/ABF, can bind to ABRE and activate ABA-dependent gene expression (see Shinozaki et al., 2003). The AREB/ABF proteins need ABA-mediated signal for their activation because of their reduced activity in the ABA-deficient *aba2* and ABA-insensitive *abi1* mutants and their enhanced activity in the ABA-hypersensitive *era1* mutant (Uno et al., 2002). This is probably due to ABA-dependent phosphorylation of the AREB/ABF proteins. Recently, transgenic plants expressing a phosphorylated form of AREB1 with multi-site mutations displayed induction of many ABA-responsive genes without exogenous ABA application (Fujita et al., 2005, Furihata et al., 2006). These data suggest that such constitutively active forms of TFs rendered by point mutations or deletion may contribute to enhancement of drought tolerance in transgenic plants (see Yamaguchi-Shinozaki and Shinozaki 2006).

The induction of the drought-inducible *RD22* gene is mediated by ABA and requires protein biosynthesis for its ABA-dependent expression (see Yamaguchi-Shinozaki and Shinozaki 2006). A MYC transcription factor, *RD22BP1 (AtMYC2)*, and a MYB transcription factor, *AtMYB2*, were shown to bind *cis*-elements in the *RD22* promoter and cooperatively activate *RD22* (Abe et al., 2003; Fig. 1). These MYC and MYB proteins are synthesized after the accumulation of endogenous ABA, which indicates their role in rather late stage of stress responses. Microarray analysis revealed target genes of MYC/MYB overexpressing transgenics, such as alcohol dehydrogenase and ABA- or jasmonic acid (JA)-inducible genes (Abe et al., 2003). Overexpression of both AtMYC2 and AtMYB2 not only revealed ABA hypersensitive phenotype but also improved osmotic-stress tolerance of the transgenic plants.

Recently, we identified drought and ABA-inducible RD26 gene encoding a NAC transcription factor (Fujita et al., 2004). RD26 NAC transcription factor gene is induced by drought, high salinity, ABA and Jasmonic acid (JA) treatment. The *RD26* overexpressing transgenic plants were hypersensitive to ABA, and the *RD26* dominant repressor overexpressing plants were insensitive to ABA. ABA- and stress-inducible genes were upregulated in the *RD26* overexpressor and repressed in the *RD26* repressor. This indicates an important role of RD26 in ABA signaling during drought stress. RD26 is also involved in defense- and senescence-related gene expression in stress response based on the microarray analysis (see Yamaguchi-Shinozaki and Shinozaki, 2006).

Transcription factors

The promoter of a drought-, high salinity- and cold-inducible gene, *RD29A/COR78/LTI78,* contains two major cis-acting elements, ABRE (ABA Responsive Element) and DRE (Dehydration Responsive Element) /CRT (C-RepeaT) involved in stress-inducible gene expression (see Shinozaki et al., 2003, Yamaguchi-Shinozaki and Shinozaki, 2006). ABRE and DRE/CRT are *cis*-acting elements that function in ABA-dependent and ABA-independent gene expression in response to abiotic stress, respectively (Fig. 1). Transcription factors belonging to the ERF/AP2 family that bind to DRE/CRT were isolated and termed *CBF/DREB1* and *DREB2* (see Yamaguchi-Shinozaki and Shinozaki, 2006). The

conserved DNA-binding motif of *DREB1A/CBF3* and *DREB2* is A/GCCGAC. The *CBF/DREB1* genes are quickly and transiently induced by cold stress, of which products activate the expression of target stress-inducible genes. The *DREB2* genes are induced by dehydration stress to express various genes involved in drought stress tolerance (Liu et al., 1998). Overexpression of *CBF/DREB1* in transgenics increased stress tolerance to freezing, drought and salt stresses, suggesting that the CBF/DREB1 proteins function in the development of cold stress tolerance without modification. Many *CBF/DREB1* target genes have been identified using both cDNA and GeneChip microarrays (Maruyama et al., 2004, Vogel et al., 2005). Most of the *CBF/DREB1* target genes contain DRE motif with (A/G)CCGACNT sequence in their promoter regions.

By contrast, overexpression of DREB2 in transgenics does not improve stress tolerance, which suggests the involvement of posttranslational activation of the DREB2 proteins (Liu et al., 1998, Sakuma et al., 2006). The DREB2 protein is expressed under normal growth conditions and activated by osmotic stress through posttranslational modification in the early stage of osmotic stress response whereas dehydration-inducible CBF/DREB1 functions in the transactivation of target stress-inducible genes just after the induction of the protein. Rice homologues for CBF/DREB1 and DREB2, 10 OsDREB1s and 4 OsDREB2s, respectively, have been identified based on rice genome sequence analyses, which function in stress-inducible gene expression in rice (see Yamaguchi-Shinozaki and Shinozaki 2006). Recently, overexpression of OsDREB1 or Arabidopsis DREB1 also improved drought and chilling tolerance in rice (Ito et al., 2006). This indicates that similar transcription factors function between dicotyledons and monocotyledons.

There are several drought-inducible genes that do not respond to either cold or ABA treatment, which suggests the existence of another ABA-independent pathway in the dehydration stress response. These genes include *ERD1* that encodes a Clp protease regulatory subunit, ClpD. The *ERD1* gene is not only induced by dehydration but also upregulated during natural senescence and dark-induced senescence (see Yamaguchi-Shinozaki, 2006). Promoter analysis of the *ERD1* gene in transgenic plant indicates that *ERD1* promoter contains cis-acting element(s) involved in not only ABA-independent stress-responsive gene expression but also senescence-activated gene expression. Promoter analysis of the *ERD1* promoter

identified two different novel cis-acting elements involved in induction by dehydration stress and dark-induced senescence. DNA-binding proteins for the cis-elements was identified to be NAC transcription factors (Tran et al., 2004).

Improvement of stress tolerance using gene transfer

Recently, many stress-induced genes with various functions are used to improve stress tolerance of plants by gene transfer of stress-inducible genes (see Bartels and Sunkar 2005, Umezawa et al., 2006a). Genes for key enzymes involved in osmolyte biosynthesis and/or detoxification have been used for the improvement of stress tolerance in transgenics plants. Used genes for transformation were *Escherichia coli* mannitol 1-phosphate dehydrogenase for mannitol, D1-pyrroline-5-carboxylate synthetase and proline dehydrogenase for proline, *Arthrobacter globiformis* choline dehydrogenase for glycine betaine, and so on (see Bartels and Sunkar 2005, Umezawa et al., 2006a).

LEA proteins and detoxification enzymes were overexpressed in transgenic plants to produce stress tolerant phenotype of the plants, which indicates that their gene products really function in stress tolerance. In all these experiments, a single gene for a protective protein or an enzyme was overexpressed under the control of the CaMV 35S constitutive promoter in transgenic plants although a number of genes have been shown to function in environmental stress tolerance and response (Bartels and Sunkar 2005, Umezawa et al., 2006a). We used a gene for galactinol synthase (GolS), a key enzyme involved in raffinose family oligosaccharide biosynthesis, for improvement of drought stress tolerance in transgenics (Taji et al., 2002).

Transcription factors have been shown to be quite useful for improvement of stress tolerance by controlling a number of target genes in transgenic overexpressors (Bartels and Sunkar, 2005, Umezawa et al., 2006a). Other regulatory factors, such as protein kinases and enzymes in ABA biosynthesis, are also useful for the improvement of stress tolerance by controlling many stress-related genes. We showed that overexpression of a gene for 9-cis-epoxycarotenoid dioxygenase (NCED), a key enzyme in ABA biosynthesis, improves drought stress tolerance in transgenics (Iuchi et al., 2001). Recently, we showed that repression of a cytochrome

P450 CYP707A3, ABA 8'-hydroxylase, involved in ABA improves drought tolerance using a T-DNA tagged mutant (Umezawa et al., 2006b).

ABA-activated SnRK2 protein kinase (OST1/SRK2E) functions in an ABA signal transduction pathway in stomata closure (Yoshida et al, 2002; Mustilli et al, 2002). SnRK2 is a member of SNF1 related PKase family, and contains 10 members in Arabidopsis. SnRK2s are activated by drought, salinity and ABA (Yoshida et al., 2002, 2006). SRK2E/OST1 is involved in stomata closure but not seed germination. SnRK2E is activated not only by ABA but also by osmotic stress, and controlled downstream of ABI1 protein phosphatase (Yoshida et al., 2006). Another SnRK2, SRK2C, is activated by osmotic stress, salt stress and ABA (Umezawa et al., 2004). SnRK2C is strongly expressed in root chip and root axis, and involved in root response to drought. SnRK2C is involved in stress-responsive gene expression to improve stress tolerance. SnRK2 protein kinases may be involved in the activation of transcription factors in osmotic-stress responsive gene expression. SRK2C is a useful tool for the improvement of stress tolerance by controlling many stress-related genes controlled by SRK2C.

Conclusion

Molecular and genomic analyses have revealed many genes that are induced by abiotic stress and their products function in stress response and tolerance in Arabidopsis and rice. Transcriptome analyses based on microarray have provided powerful tools in gene discovery of stress-responsive genes from various crops and trees. Transgenic plants with antisense or RNAi constructs, and T-DNA- or transposon-tagged mutants are used to analyze their function based on phenotypes due to loss-of-function of genes. Moreover, transgenic overexpressors are also useful not only for the functional analyses of genes but also for improvement of stress tolerance by gene transfer (Bartels and Sunkar, 2005, Umezawa et al., 2006a). Combination of molecular, genomic and genetic analyses will elucidate complex regulatory systems in abitoic stress-responsive gene expression. Arabidopsis stress related genes are useful not only in improvement of abiotic stress tolerance in transgenic crops and trees but also in discovery of stress-related genes of various crops and trees based comparative genomics.

References

1. Abe H, Urao T, Ito T, Seki M, Shinozaki K, Yamaguchi-Shinozaki K. 2003. Arabidopsis AtMYC2 (bHLH) and AtMYB2 (MYB) function as transcriptional activators in abscisic acid signaling. Plant Cell. 15. 63-78.
2. Bartel D, Sunkar. 2005. Drought and salt tolerance in plants. Critical Review in Plant Science. 24. 23-58.
3. Fujita M, Fujita Y, Maruyama K, Seki M, Hiratsu K, Ohme-Takagi M, Tran LSP, Yamaguchi-Shinozaki K, Shinozaki K. 2004. A dehydration-induced NAC protein, RD26, is involved in a novel ABA-dependent stress-signaling pathway. Plant Journal. 39. 863-876.
4. Fujita Y, Fujita M, Satoh R, Maruyama K, Parvez MM, Seki M, Hiratsu K, Ohme-Takagi M, Shinozaki K, Yamaguchi-Shinozaki K. 2005. AREB1 is a transcription activator of novel ABRE-dependent ABA signaling that enhances drought stress tolerance in Arabidopsis. Plant Cell. 17. 3470-88.
5. Furihata T, Maruyama K, Fujita Y, Umezawa T, Yoshida R, Shinozaki K, Yamaguchi-Shinozaki K. 2006. Abscisic acid-dependent multisite phosphorylation regulates the activity of a transcription activator AREB1. Proceedings of the National Academy of Sciences. USA. 103. 1988-93.
6. Ito Y, Katsura K, Maruyama K, Taji T, Kobayashi M, Seki M, Shinozaki K, Yamaguchi-Shinozaki K. 2006. Functional analysis of rice DREB1/CBF-type transcription factors involved in cold-responsive gene expression in transgenic rice. Plant & Cell Physiology 47. 141-53.
7. Iuchi S, Kobayshi M, Taji T, Naramoto M, Seki M, Kato T, Tabata S, Kakubari Y, Yamaguchi-Shinozaki K, Shinozaki K. 2001 Regulation of drought tolerance by gene manipulation of 9-cis-epoxycarotenoide, a key enzyme in abscisic acid biosynthesis in Arabidopsis. Plant Journal. 27. 325-333.
8. Liu Q, Sakuma Y, Abe H, Kasuga M, Miura S, Yamaguchi-Shinozaki K, Shinozaki K. 1998. Two transcription factors, DREB1 and DREB2, with an EREBP/AP2 DNA binding domain, separate two cellular signal transduction pathways in drought- and low temperature-responsive gene expression, respectively, in Arabidopsis. Plant Cell. 10. 1491-1406.
9. Maruyama K, Sakuma Y, Kasuga M, Ito Y, Seki M, Goda H, Shimada Y, Yoshida S, Shinozaki K, Yamaguchi-Shinozaki K. 2004. Identification of cold-inducible downstream genes of the Arabidopsis DREB1A/CBF3 transcriptional factor using two microarray systems. Plant Journal. 38. 982-993.
10. Mustilli AC, Merlot S, Vavasseur A, Fenzi F, Giraudat J. 2002. Arabidopsis OST1 protein kinase mediates the regulation of stomatal aperture by abscisic acid and acts upstream of reactive oxygen species production. Plant Cell. 14. 3089-3099.
11. Nambara E, Marion-Poll M. 2005. Abscisic acid biosynthesis and catabolism. Annual Review of Plant Biology. 56. 165-185.
12. Sakuma Y, Maruyama K, Osakabe Y, Qin F, Seki M, Shinozaki K, Yamaguchi-Shinozaki K. 2006. Functional analysis of an Arabidopsis transcription factor, DREB2A, involved in drought-responsive gene expression. Plant Cell. 18. 1292-309.

13. Shinozaki K, Yamaguchi-Shinozaki K, Seki M. 2003. Regulatory network of gene expression in the drought and cold stress responses. Current Opinion in Plant Biology 6. 410-417.
14. Taji T, Ohsumi C, Iuchi S, Seki M, Kasuga M, Kobayashi M, Yamaguchi-Shinozaki K, Shinozaki K. 2002. Important roles of drought- and cold-inducible genes for galactinol synthase in stress tolerance in Arabidopsis thaliana. Plant Journal. 29. 417-426.
15. Tran LSP, Nakashima K, Sakuma Y, Simpson SD, Fujita Y, Maruyama K, Fujita M, Seki M. Shinozaki K, Yamaguchi-Shinozaki K. 2004. Isolation and functional analysis of Arabidopsis stress-inducible NAC transcription factors that bind to a drought-responsive cis-element in the early responsive to dehydration stress 1 promoter. Plant Cell. 16. 2481-2498.
16. Umezawa T, Fujita M, Fujita Y, Yamaguchi-Shinozaki K, Shinozaki K. 2006a. Engineering Drought Tolerance in Plants: Discovering and Tailoring Genes Unlock the Future. Current Opinion in Biotechnology. 17. 113-122
17. Umezawa T, Okamoto M, Kushiro T, Nambara E, Oono Y, Seki M, Kobayashi M, Koshiba T, Kamiya Y, Shinozaki K. 2006b. CYP707A3, a major ABA 8'-hydroxylase involved in dehydration and rehydration response in Arabidopsis thaliana. Plant J. 46. 171-82.
18. Umezawa T, Yoshida R, Maruyama K, Yamaguchi-Shinozaki K, Shinozaki K. 2004. SRK2C. a SNF1-related protein kinase 2, improves drought tolerance by controlling stress-responsive gene expression in Arabidopsis thaliana. Proceedings of the National Academy of Sciences. 101. 17306-17311.
19. Uno Y, Furihata T, Abe H, Yoshida R, Shinozaki K, Yamaguchi-Shinozaki K. 2000. Arabidopsis basic leucine zipper transcriptional transcription factors involved in an abscisic acid-dependent signal transduction pathway under drought and high-salinity conditions. Proceedings of the National Academy of Sciences. 97. 11632-11637.
20. Vogel JT, Zarka DG, Van Buskirk HA, Fowler SG, Thomashow MF. 2005. Roles of the CBF2 and ZAT12 transcription factors in configuring the low temperature transcriptome of Arabidopsis. Plant Journal 412. 195-211.
21. Yamaguchi-Shinozaki K. Shinozaki K. 2006. Transcriptional regulatory networks in cellular responses to dehydration and cold stresses. Annual Review of Plant Biology. 57. 781-803.
22. Yoshida R, Hobo T, Ichimura K, Mizoguchi T, Takahashi F, Alonso J, Ecker JR, Shinozaki K. 2002. ABA-activated SnRK2 protein kinase is required for dehydration stress signaling in Arabidopsis. Plant Cell Physiology 43. 1473-1483.
23. Yoshida R, Umezawa T, Mizoguchi T, Takahashi S, Takahashi F, Shinozaki K. 2006The regulatory domain of SRK2E/OST1/SnRK2.6 interacts with ABI1 and integrates abscisic acid (ABA) and osmotic stress signals controlling stomatal closure in Arabidopsis. Journal of Biological Chemistry. 281. 5310-8.
24. Zhang JZ, Creelman RA, Zhu JK. 2004. From laboratory to field. Using information from Arabidopsis to engineer salt, cold, and drought tolerance in crops. Plant Physiology. 135. 615-621.

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The Scope of Gene Technologies in Improving Drought Tolerance in Crops

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Introduction

The International Crops Research Institute for the Semi-Arid Tropics (ICRISAT) is one of the 15 Future Harvest Research centres, led by the Consultative Group on International Agriculture Research (CGIAR). Headquartered in India with two regional hubs in Niger (for West Africa) and Kenya (for East/Southern Africa) and mandate for the semi-arid tropics, ICRISAT deals with five mandate crops commonly grown in the region: Chickpea, groundnut, pigeonpea, pearl millet and sorghum. For obvious reasons, drought is at the center of the research and development agenda of ICRISAT. Its major objective is to develop resilient crops to low and erratic rainfall.

Water deficit is the most prominent abiotic stress, which limits severely crop yields and opportunities to improve livelihoods of poor farmers in the

semi-arid tropics. For instance, it is estimated that drought is responsible for $ 520 million loss per year in groundnut only (Subbarao et al., 1995). Therefore, major efforts are needed to improve the tolerance of crops to water deficit, and there is now increasing hope that this would be possible. For instance, from the estimated 3.7 million tones loss annually in chickpea from water deficit, about 2.1 million tones could be recovered from crop improvement efforts and similarly half of the loss in groundnut (Johansen and Nigam, 1994).

Yet, drought is a complex issue, which involves a number of agronomic, edaphic and climatic aspects. Although drought can be broadly characterized by its timing, duration, and intensity, the breeding of drought tolerant varieties through conventional breeding remains difficult, in particular because of the large genotype by environment interactions. This is in part because yield is the combination of different traits whose relative importance usually varies a lot in different types of environment. A common success has been achieved across the different mandate crops by breeding early maturing varieties, which are able to escape the drought and mature before the water deficit becomes too severe.

Yet, further improvements under water deficit are still needed. A trait-based approach has been considered to dissect yield under drought into its different components. In that approach, we try to follow a simple model defined by (Passioura, 1977), where yield (Y) is defined as T x TE x HI, where T represents how much water is taken up by roots, TE (transpiration efficiency) represent how efficiently the transpired water is converted into biomass, and HI (harvest index) represents how the biomass is converted into grain. To identify contrasting parents for these traits, we also screen large numbers of representative germplasm utilizing representative subsets of germplasm (Upadhyaya and Ortiz, 2001). A trait-based approach has yielded some success for some abiotic stresses (Hall, 1992; Condon et al., 2002; Sinclair et al., 2000). However, some of these traits are not easily measurable and remain difficult to pyramid in a similar background. Recent advances in molecular genetics now allow identifying quantitative trait loci (QTLs) related to those traits. Linked to molecular markers that can be easily pinpointed, these QTLs could now be pyramided, and this would make the molecular breeding of drought tolerant crops possible (Ribaut et al., 1996).

In certain crops, a transgenic approach has been used as an attempt to speed up the process of molecular introgression of putatively beneficial genes. This approach could be a valid one in those crops that have received little attention from molecular studies and which do not have sufficient set of tools to undertake molecular breeding. This is for instance the case in groundnut, the lack of genetic polymorphism, a bottleneck during the evolution of peanut, makes it difficult to breed through molecular approaches. However, a single-gene transgenic approach could be criticized because abiotic stress tolerance involves very likely many genes. So, it has been suggested that a wiser approach could be the use of transcription factors, i.e. major "switch" that trigger a cascade of genes in response to a given stress (Chinnusamy et al., 2004). This approach has been undertaken at ICRISAT.

The objective of this paper was to make an update drought research at ICRISAT, to highlight the major achievements of the past years, and to give an insight of the major current research orientations, in particular in marker-assisted selection (MAS). In this review, we will not address drought escape mechanisms.

Marker Assisted Breeding in Pearl Millet

Pearl millet is a well-adapted plant to semi-arid areas and is subjected to post-flowering stress, for which the major focus is currently on terminal drought tolerance. Yet, improvement of its performance under drought conditions remains possible. It was found that the performance of pearl millet under water deficit were in part explained by the yield potential under water deficit and the drought escape mechanism. Therefore, a drought resistance index (DRI) was calculated by Bidinger et al. (1987) to identify source of tolerance to drought. The criterion that was the most related to the DRI was the panicle harvest index (PNHI), and this criterion is now used to screen tolerant accessions.

Crosses have been made between genotypes having high and low PNHI and the genotyping and phenotyping of testcross hybrids of the progenies have led to the identification of QTLs for terminal drought tolerance in multi-location trials. A major QTL has been identified on linkage group 2 of pearl millet. The existence of that QTL has also been confirmed using another cross between tolerant/sensitive genotypes (Yadav et al., 2004). In

short, that QTL contributes to a larger number of florets setting grains on the panicle, and to a better grain filling, both contributing to a higher PNHI (Figure 1). That QTL is currently the major focus of research. It has been introgressed in the background of terminal drought sensitive genotype H77/833-2 and after several round of backcrosses, several introgression lines such as ICMR 01029 or ICMR 01031, have been identified with superior terminal drought tolerance (Hash et al., 2005).

Recent work has tested some of the QTL introgression lines, along with contrasting parents and tends to conclude that more profuse rooting in the deeper soil layer may be a major underlying factor to that QTL (Vadez et al., 2005). Current efforts are now being put on pyramiding that QTL on LG2 with downy mildew resistance QTL. Efforts are also being made to further characterize the role of roots in that QTL, and possibly to identify QTLs for root traits in pearl millet.

Marker Assisted Breeding in Sorghum for Staygreen

Sorghum is a dual-purpose (grain + straw) crop adapted to the semi-arid tropics and subtropics. Sorghum is increasingly grown during the post-rainy season and is therefore dependent on stored soil moisture, for which it is commonly exposed to terminal drought conditions, usually starting around flowering. The extension of leaf greenness in sorghum, i.e. the stay-green trait, has been described as an important secondary trait involved in yield improvement under terminal drought stress (Borell and Hammer, 2000). The maintenance of green leaves is related to a delay of nitrogen remobilisation from leaves, which maintains photosynthetic activity during grain filling. Under terminal drought conditions, a sustained photosynthesis allows a continued supply of carbohydrate to the developing grains. It was recently shown that staygreen expression was correlated to the 100-seed weight, a good proxy for grain filling (Bidinger, personal communication). Staygreen is evaluated by following the pattern of leaf senescence under terminal drought conditions after flowering. In short, several plants are tagged in each plot and the top 6 leaves are scored weekly for their percentage of green leaf area (GLA). The comparison of the pattern of GLA retention allows identifying staygreen from senescent materials (Figure 2).

Several QTLs have been found for staygreen from different crosses (Crasta et al., 1999; Haussman et al., 2002) from which 4 major QTLs have been identified. At ICRISAT, the sorghum molecular breeding group has been focusing on staygreen QTLs stg1, stg3, stg4, and stgB, using the donor parent B35. Introgression lines have been produced from two cycles of backcrossing and MAS selection for different combinations of the staygreen QTLs described above. Because B35 has poor adaptation to tropical environment, the introgression has been hampered by a lot of "linkage drag" and those lines have not been able to outperform the elite drought sensitive parents R16 and ISIAP Dorado. However, 2 of the introgression lines already produce larger forage quantities than and have better forage quality (higher N content and better digestibility).

The current focus of work is therefore to remove the linkage drag associated with the use of B35 as a donor parent. To do so, two more backcrosses assisted by markers for the 4 QTLs have been performed to recover most of the genome of the recurrent parent R16 on the most promising introgression lines. These materials will be tested in the forthcoming season at ICRISAT (2006-07). To exclude from the introgressed QTLs those genes that are tightly linked to the QTL and which confer poor agronomic or quality characteristics, more markers are needed in the vicinity of the targeted QTL. In parallel, we have tested whether root traits would have any underlying role in the staygreen trait. We have evaluated the root growth of 2 staygreen donor parents, B35 and E36-1 and two sensitive parents R16 and ISIAP Dorado, in 2.0 m long, 18 cm diameters PVC cylinders. We have found that under water deficit both staygreen parents had roots about 60 cm deeper than senescent materials whereas under well-watered conditions, the rooting depth of all genotypes did not differ (Vadez et al., 2005).

Mapping Root Traits in Chickpea

Chickpea is exclusively grown during the post-rainy season, which coincides with the cool days of the year. As major chickpea cultivation areas are rain fed environments, Chickpea exclusively depends on store moisture and, therefore, faces terminal drought conditions. Roots have been a major focus of research for over a decade at ICRISAT. It has been

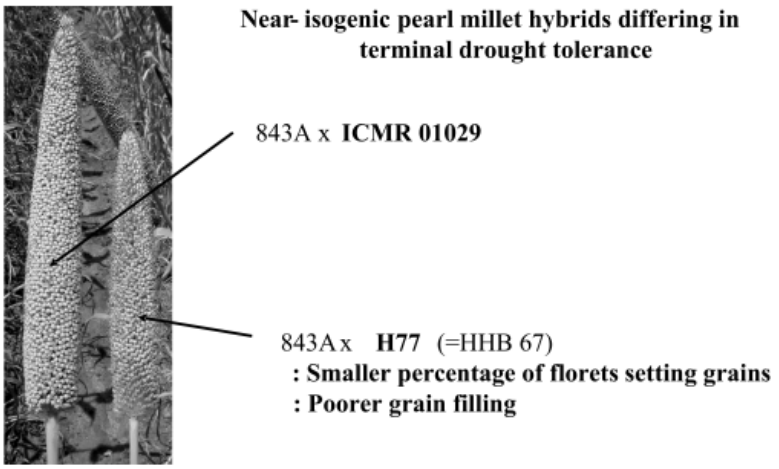

Figure 1. Typical difference in the panicle of a terminal drought tolerant genotypes ICMR 01029 x 843 A: A higher number of florets setting grains and a better grain filling, both ontributing to higher PNHI (panicle harvest index).

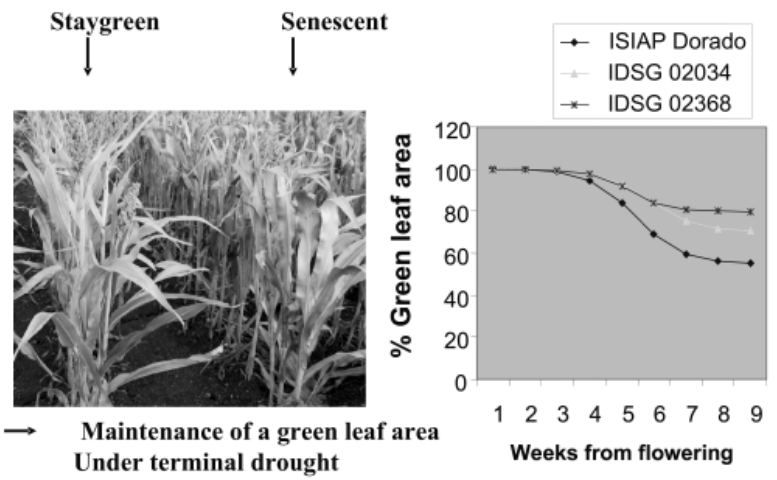

Figure 2. Typical appearance of the stay green trait in field conditions under terminal drought, i.e. a delayed leaf senescence, and a typical pattern of green leaf area (GLA) retention over time between introgression lines and senescent parent ISIAP Dorado.

found that deep and more profuse rooting was a direct contributor to the seed yield under terminal drought (Kashiwagi et al., 2006). However, the methods used to assess root traits have only improved in the past few years (Kashiwagi et al., 2005 & 2006), where roots are now assessed in 1.2 m long, 18 cm diameter PVC cylinders. Roots used to be digged out from field conditions, using the monolith method, an extremely time-consuming method. A good agreement between field and cylinder data has been found (Kashiwagi, 2006). Using the PVC cylinder method, the range of genetic variation for root trait has been recently explored using a large representative set of genotypes, including the mini-core collection of ICRISAT (10 per cent of core collection, 1 per cent of entire collection) (Upadhyaya and Ortiz, 2001). From that screening, more contrasting genotypes for root traits have been identified and new mapping populations developed from parents showing more root contrasts that those used previously (Figure 3) (Kashiwagi et al., 2005).

The current focus of research is now to phenotype the different populations. From the initial population between Annigeri (shallow roots) and ICC4958 (deep and profuse roots, a QTL accounting for over 30 per cent of the variation in root length density has been found (Chandra et al., 2004). The phenotyping and genotyping of two recent populations is under way (ICC1882 x ICC4958 and ICC283 x ICC8261) and there is good scope to find more QTLs for root traits in chickpea. Next step toward MAS breeding in chickpea would be to start their introgression into locally adapted varieties.

A Transgenic and Marker-Assisted Approach in Groundnut for TE

Groundnut is usually grown under rain fed conditions and is often exposed to erratic rainfall pattern, which exposes the crop to intermittent drought spells at every stage of crop development. For that reason, the major focus of research is to develop varieties that are able to efficiently use erratic amounts of water, having therefore high transpiration efficiency (TE). Genetic variability for TE has been found in groundnut (Wright et al., 1994). Unfortunately, an attempt to integrate the TE traits into varieties using a trait-based approach has been only equally successful

than following a conventional approach. This has been mostly because of the difficulty to pyramid high TE and high HI in a similar background, i.e. genotypes having high TE usually had low harvest index (HI) (Wright et al., 1991).

Yet, contrasting parents have been identified and mapping populations developed. One such population has been phenotyped for TE and shows good and consistent segregation across seasons. Our current major limitation for mapping QTLs linked to TE trait is to genotype that population with a sufficient number of polymorphic markers. Groundnut is one such crop that probably results from a single event of hybridization between two wild ancestors. This has isolated groundnut from its wild progenitors and has created a genetic bottleneck characterized with the lack of genetic polymorphism between most of the cultivated germplasm. In collaboration with EMBRAPA (Brazil), we are currently trying to re-synthesize groundnut from its wild progenitors, as an attempt to re-introduce genetic polymorphism. Alternatively, we are also trying to develop more markers for cultivated groundnut, in particular exploring new molecular techniques to generate novel types of polymorphic markers such as DArTs.

Since the molecular breeding approach in groundnut is bound on the success of finding a sufficient number of markers, a transgenic approach has been attempted in groundnut to introgress genes putatively involved in drought tolerance. Instead of using a single gene, the genetic transformation laboratory of ICRISAT has introgressed a transcription factor, DREB1A, using rd29 as a stress responsive promoter, into JL24, a popular groundnut variety in India. The testing of 5 events in T3 generation, after an initial screening of 14 events, has revealed that most transgenics had higher TE than the non transformed parent under well watered conditions, and that one event had higher TE than the non transformed parent across moisture conditions (Table 1) (Vadez et al., 2005). These results are very encouraging because the range of variation for TE between the transgenics and the parent was higher than what has been found with a RIL population. Further, the fact that transgenic events showing such large phenotypic contrast, while being isogenic for one inserted gene, provides great opportunities to re-investigate the mechanisms underlying high TE in groundnut.

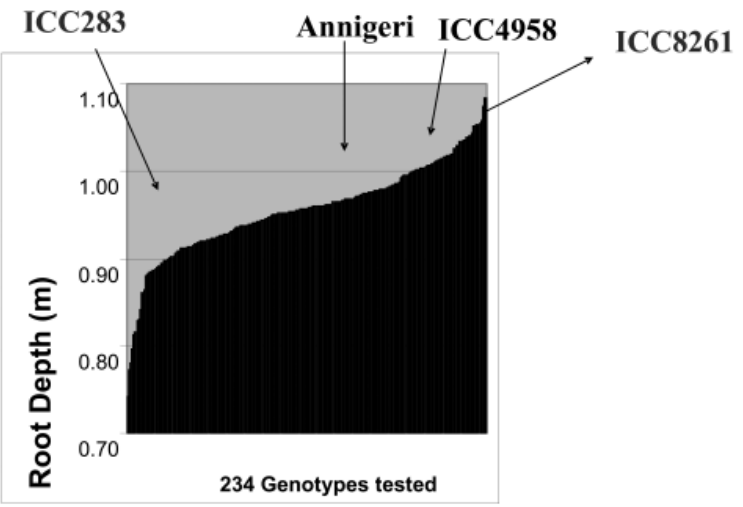

Figure 3. Range of genotypic variation for root traits in 234 genotypes, including the mini-core collection. Data show the genotypes involved in the newly developed mapping populations.

Table 1. Transpiration efficiency (TE, in g biomass kg^{-1} water transpired) in 5 transgenic events and the untransformed parent JL 24, under well-watered (WW) and drought stressed conditions (DS). Pooled data fro 2 replicated experiments.

	TE (WW)	TE (DS)
JL 24	2.05 [b]	4.29 [b]
RD 19	4.31 [a]	4.99 [b]
RD 12	5.13 [a]	4.63 [b]
RD 20	3.19 [b]	4.52 [b]
RD 2	4.09 [a]	6.12 [a]
RD 11	4.96 [a]	5.59 [a]

Conclusion

Although major progresses have been made to breed drought adapted varieties, mainly by breeding for earliness, efforts need to be made to further improve drought tolerance and thereby increase and stabilize yield

in drought-prone areas. The advent of molecular breeding now gives the possibility to identify molecular markers for traits contributing to drought tolerance. The progresses made in the cereals at ICRISAT, in particular pearl millet for which the first products of marker-assisted selection have been produced, is particularly encouraging and give hope that similar success could be reached in other crops. In sorghum, hope is high that same success would occur in the next few years.

In the legumes, molecular breeding is lagging behind because chickpea and groundnut have not received as much attention as the cereals. Molecular breeding of root traits should be possible in the next few years in chickpea, once several other major QTLs for root traits are identified from the newly developed mapping populations. The situation is a little more remote in groundnut where the lack of markers still limits the possibility to map traits of interest. Recent progresses in developing synthetic amphidiploids, i.e. re-synthesized groundnut, should help circumvent the lack of genetic diversity, and could possibly reintroduce beneficial alleles in the background of cultivated groundnut. Current efforts are also being made to develop a new generation of more polymorphic markers to fully saturate the genetic maps of groundnut. There, the transgenic option might be a technical alternative, provided the choice of insert is judicious and evaluation of event made with care and sense.

In the end, results obtained in the cereals at ICRISAT give evidence that MAS breeding is possible. Yet, what appears from all crops is that the introgression of beneficial QTL is likely to always be accompanied by lots of linkage drag. The solution to this is to develop more markers in the vicinity of targeted QTLs, which is always going to be a difficult, time-consuming, and costly challenge.

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References

1. Bidinger, F.R., Mahalakshmi, V. and Rao, G.D.P. 1987. Assessment of drought resistance in pearl millet [Pennisetum americanum (L.) Leeke]. I. Factors affecting yield under stress. Australian Journal of Agricultural Research. 38, pp37-48.
2. Borrell, A.K. and Hammer, G.L. 2000. Nitrogen Dynamics and the Physiological Basis of Stay-Green in Sorghum. Crop Science. 40, pp1295-1307
3. Chandra S., Buhariwalla, H.K., Kashiwagi, J., Harikrishna, S., Sridevi, R.K., Krishnamurthy, L., Serraj, R. and Crouch, J.H. 2004. Identifying QTL-linked Markers in marker-deficient Crops. In: Fischer T etal (2004). New directions for a diverse planet: Proceedings for the 4th International Crop Science Congress, Brisbane, Australia.
4. Chinnusamy,V., Jagendorf, A. and Zhu, J.K. 2005. Understanding and Improving Salt Tolerance in Plants. Crop Sci. 45, pp437–448.
5. Condon, A.G. et al., 2002. Improving intrinsic water-use efficiency and crop yield. Crop Sci. 42, pp122-131.
6. Crasta, O.R., Xu, W.W., Rosenow, D.T., Mullet, J. and Nguyen, H.T. 1999. Mapping of post-flowering drought resistance traits in grain sorghum: association between QTLs influencing premature senescence and maturity. Mol Gen Genet. 262, pp579-588.
7. Hall, A.E. 1992. Breeding for heat tolerance. Plant Breed Rev. 10, pp129-168.
8. Hash, C.T, Rizvi, S.M.H., Serraj, R., Bidinger, F.R., Vadez, V., Sharma, A., Howarth, C.J. and Yadav, R.S. 2005. Field Assessment of Backcross-derived Hybrids Validates a Major Pearl Millet Drought Tolerance QTL. Paper presented at the Crop Science Society of America Congress, Seattle.
9. Haussmann, B.I.G., Mahalakshmi, V., Reddy, B.V.S., Seetharama, N., Hash, C.T. and Geiger, H.H. 2002a. QTL mapping of stay-green in two sorghum recombinant inbred populations. Theoretical and Applied Genetics. 106, pp133-142.
10. Johansen, C. and Nigam, S.N. 1994. Importance of drought stress and its alleviation in legumes. Crop Sci. 24, pp17-19.
11. Kashiwagi, J., Krishnamurthy, L., Crouch, J.H. and Serraj, R. 2006a. Variability of root characteristics and their contributions to seed yield in chickpea (Cicer arietinum L) under terminal drought stress. Field Crops Res. 95, pp171-181.
12. Kashiwagi, J., Krishnamurthy, L., Serraj, R., Upadhyaya, H.D., Krishna, S.H., Chandra, S. and Vadez, V. 2006b. Genetic variability of drought-avoidance root traits in the mini-core germplasm collection of chickpea (Cicer arietinum L.). Euphytica (In press).
13. Passioura, J.B. 1977. Grain yield, harvest index and water use of wheat. J. Aust. Inst Agric. Sci. 43, pp21.
14. Ribaut, J.M., Hosington, D.A., Deitech, J.A., Jiang, C. and Gonzalex-de-Leon, D. 1996. Identification of quantitative trait loci under drought conditions in tropical maize. 1. Flowering parameters and the anthesis-silking interval. Theor. Appl. Genet. 92, pp905-914.

15. Sinclair, T.R. et al., 2000. Identification of soybean genotypes with nitrogen fixation tolerance to water deficit. Crop Sci. 40, pp1803-1809.
16. Subbarao, G.V., Johansen, C., Slinkard, A.E., Nageshwara Rao, R.C., Saxena, N.P. and Chauhan, Y.S. 1995. Strategies for improving drought resistance in grain legumes. Crit. Rev. Plant Sci. 14, pp469-523.
17. Upadhyaya, H.D. and Ortiz, R. 2001. A mini core subset for capturing diversity and promoting utilization of chickpea genetic resources in crop improvement. Theo. Appl. Genet. 102, pp1292-1298.
18. Vadez, V., Kashiwagi, J., Krishnamurthy, L., Serraj, R., Sharma, K.K., Devi, J., Bhatnagar-Mathur, P., Hoisington, D., Chandra, S., Gaur, P.M., Nigam, S.N., Rupakula, A., Upadhyaya, H.D., Hash, C.T. and Rizvi, S.M.H. 2005. Recent advances in drought research at ICRISAT: Using root traits and rd29a::DREB1A to increase water use and water use efficiency in drought-prone areas. Poster presented at the Interdrought II conference, Rome.
19. Wright, G.C., Hubick, K.T. and Farquhar, G.D. 1991. Physiological analysis of peanut cultivar response to timing and duration of drought stress. Aust. J. Agric. Res. 42, pp453-70.
20. Wright, G.C., Nageswara Rao and Farquhar, G.D. 1994. Water use efficiency and carbon isotope discrimination in peanut under water deficit conditions. Crop Science 34, pp92-97.
21. Yadav, R.S., Hash, C.T., Bidinger, F.R., Devos, K.M. and Howarth. 2004. Genomic regions associated with grain yield and aspects of post-flowering drought tolerance in pearl millet across stress environments and tester background. Euphytica 136, pp265-277.

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NEW DIRECTIONS IN SCIENCE AND INNOVATION POLICY

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Freedom to Innovate: Biotechnology in Africa's Development

Calestous Juma and Ismail Serageldin

It is no secret that Africa's history has been marked by a development narrative in which the benefits from science, technology and innovation have been enjoyed by few, instead of being seen as tools for the development of all citizens. Today this is changing and Africa's leaders view science, technology and innovation as critical to human development, global competitiveness and ecological management.

'Biotechnology', if used in the most comprehensive sense of that word, includes technologies that operate at the level of genes, but it also includes non-genetic biological technologies. Biotechnologies need to be developed with appropriate safeguards in place and according to the best internationally-agreed standards.

Individual countries in central, eastern, western, northern and southern Africa to work together at the regional level to scale up the development of biotechnology. A key vehicle is through what we call Regional Innovation Communities and Local Innovation Areas. These would include clusters of expertise, sharing knowledge, creative ideas, personnel, and working on problems and projects collaboratively. Regional Innovation Communities might include institutions that are already situated close together, such as universities, science-based industry and science parks. But today, institutions do not need to be in close proximity to work together. Effective and

successful collaboration can take place between people and institutions that are geographically separate so long as the will exists to do so.

Regional Innovation Communities are a form of regional economic integration, which Africa is already experiencing in other areas. Regional economic integration more broadly can be an institutional vehicle for mobilizing, sharing and using existing scientific and technological capacities, including human and financial resources as well as physical infrastructure for R&D and innovation.

Some Regional Innovation Communities will come about organically. But many will need to be nurtured. In every case, what will be needed is a pool of talented and skilled people, as well as new and existing institutions willing and able to embrace change. There needs to be a step-change in this area, which will entail reviewing and adjusting national and regional policies and related legislation to provide an environment conducive for higher education, R&D and innovation.

We also suggest priority areas in biotechnology that are of relevance to Africa's development. Identifying critical capabilities needed for the development and safe use of biotechnology. Appropriate regulatory measures needed, that can advance research, commercialization, trade and consumer protection. Strategic options for creating and building regional biotechnology innovation communities and local innovation areas in Africa.

Priority Areas in Biotechnology

Food security, nutrition, healthcare and environmental sustainability are among Africa's biggest challenges. Regional biotechnology efforts have a role to play in each and can be implemented through what the panel calls long-term 'biotechnology missions'. Clustering can take place around priority areas as well as in places and institutions where expertise exists.

Health biotechnology, for example, is concentrated in southern Africa, for example. North Africa is established in bio-pharmaceuticals. Animal biotechnology has strong roots in east Africa; crop biotechnology in the west and forest biotechnology in central Africa.

Strengthening Critical Capacities

Africa's ability to effectively use existing and emerging biotechnologies will depend largely on the level of investment in building physical, human, institutional and societal capacities. More specifically, Africa's regional innovation communities will need to specifically focus on creating and reforming existing knowledge-based institutions, especially universities, to serve as centres of diffusion of new technologies into the economy. Development cooperation will need to shift from dependence on relief models to a new emphasis on competence-building. Investing in critical capabilities is central to Africa's ability to benefit from its resources.

Africa needs to: develop and expand national and regional human resources development strategies that include: (1) a continental biotechnology curriculum that focuses on specific areas and targets that offer high economic potential for the regions and the continent; (2) a consortium of clearly identified and designated universities that develop and offer regional biotechnology training courses; (3) a focus on female recruitment in the sciences and engineering.

Africa needs to immediately expand and create infrastructure development programs that upgrade strategically important infrastructure in order to tap into the opportunities that may arise from biotechnology. Research and development activities for the development, operation and maintenance of infrastructure needs to be promoted, and linkages need be established with both domestic and overseas research networks. African countries need to identify specific biotechnology priority areas that offer high potential for regional R&D and product development and integrate these priorities into African regionalization processes and policies.

To improve commercialization and business capacity, Africa needs to: (1) foster R&D cooperative partnerships at the local, regional and international levels; (2) create policy instruments that enable business incubation and development; (3) develop functional market infrastructure for economic development; and (4) stress the role of technology in general and biotechnology in particular for SME development policy.

The following mechanisms can be instituted to increase the available funding for biotechnology R&D in Africa: (1) substantially increased national R&D budgets; (2) special funding mechanisms, possibly innovation funds funded through a variety of means including challenge funds; (3)

specific funding mechanisms under government ministries; (4) distinct African funding schemes or facilities; (5) reformed tax law (i.e. foundation laws and industry-wide levies); and (6) national lotteries.

Better Governance for Biotechnology

Africa should adopt the co-evolutionary approach where consumer protection goes hand in hand with the development of the technology itself. New stakeholder partnerships, awareness campaigns, and innovation competitions need to be created to facilitate public awareness and education on issues of biotechnology.

Emphasis should be put on maximizing the risks associated with new technologies while reducing their negative impacts. Equally important is a consideration of the long-term implications of non-adoption of emerging technologies. The essential point therefore is developing and harmonizing regional regulations governing issues such as regional integration, research and development, safety (covering field and clinical trials) and trade in biotechnology products and services.

Africa's regulatory institutions need transparent and high quality scientific capacity to assess biotechnology-related risks and to be able to regulate quickly, safely and effectively. APB recommends the creation of an African presidential science and innovation council of to oversee the implementation of AU recommendations related to scientific capacity building. Complementary organs may also need to be created in the Regional Innovation Communities. There is a need to develop harmonized legislation and measures based on international, continental, and individual country good practices in the context of the emerging Regional Innovation Communities. Development of such frameworks can lead to a co-evolution of regulatory frameworks and technology development.

The Pan-African Parliament (PAP) is an ideal institutional locus for harmonizing regulations and promoting biotechnology missions. There is need to strengthen PAP engagement in developing regional and continental programmes for biotechnology. Strengthening it will involve establishing for it advisory mechanisms, providing its committee with evidence-based policy studies, and equipping it with technology monitoring capabilities.

Strategic Considerations for the Future

Africa needs to take strategic measures aimed at promoting the application of modern biotechnology to regional economic integration and trade. Such measures include fostering the emergence of regional innovation systems in which biotechnology-related Local Innovation Areas play a key role. But doing so will entail a diversity of complementary measures that include upgrading regional capacities and forging international partnerships. Furthermore, funding such initiatives will involve adopting a wide range of approaches aimed at generating the necessary financial resources, including innovation funds. Existing funding sources such as international and regional development banks could also play a key role in helping in the commercialization of products from the biotechnology-related Local Innovation Areas. Emphasis will therefore be put on technology prospecting to identify worldwide and commercialize technologies in Africa.

Regional Economic Communities need to begin to determine potential opportunities for biotechnology specialization and foster regional networking of biotechnology centres for R&D related to this regional specialization. African Regional Innovation Communities need to facilitate North-South and South-South collaborations as well as mobilize the expertise its diaspora for development.

Long-term process of biotechnology development in Africa needs to go hand-in-hand with the creation of regional economies. African countries need to (a) facilitate the process of regional integration; and (b) foster technological innovation as a force for promoting regional integration and trade

Local Innovation Areas hold the promise of creating competitive, biotechnology-driven African economies that benefit from spatial concentrations of regional innovation actors (universities, firms, and research institutes) Countries and Regional Innovation Communities need to (a) identify biotechnology-related fields of local relevance; and (b) facilitate local innovation centre upgrading initiatives for development. There is great potential in developing North-South and South-South collaborations supporting biotechnology R&D and capacity-building in African Regional Innovation Communities and Local Innovation Areas.

Countries and emerging Regional Innovation Communities need to identify ways of improving cooperation with other regions (particularly Asia and Latin America) of the world to effectively address issues pertaining to biotechnology.

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Agricultural R&D Spending at a Crossroads

Philip Pardey, Julian Alston, Nienke Beintema

Introduction

Throughout the 20th century, improvements in agricultural productivity have alleviated poverty and starvation and fuelled economic progress. These productivity improvements have been closely linked to investments in agricultural research and development (R&D). However, in the past 25 years many countries have made major changes to the ways they fund and organise public agricultural R&D, and the incentives affecting private R&D. These changes raise questions about the prospects for sustaining productivity growth over the next 25 years and beyond. Early indicators suggest that a global slowdown in farm productivity may have already begun.

Agricultural R&D Trends

In the past, both developing and developed countries have been dependent on technology spillovers from a few of the world's affluent countries, both directly and through the system of International Agricultural Research Centres (IARCs), including the Consultative Group on International Agricultural Research (CGIAR). However, this trend changed towards the end of the 20th century in many countries, with public and private roles

shifting. Support for public agricultural R&D slowed, especially for near-market, applied, productivity-enhancing research. In the world's most affluent countries, which traditionally provided the majority of the world's agricultural R&D investments, a slower growing, stagnant, or shrinking pool of public agricultural R&D funding is increasingly being diverted away from the traditional agenda towards environmental objectives, food quality and safety, and other objectives.

These changes mean that many countries (and especially developing countries) may have to become more self-reliant in the development of applicable agricultural technologies. Complete self-reliance will be beyond many countries, especially given recent and ongoing structural changes in science and scientific institutions, in particular the rise of modern biotechnologies and other high-tech agriculture, and the associated role of intellectual property (IP). The largest developing countries (Brazil, China and India) are making the transition; nevertheless, they have yet to overcome the problem of chronic underinvestment in agricultural R&D, and they have many problems to overcome with respect to the effective management and efficient use of their available resources.

The most disadvantaged countries will continue to rely on the supply of spillovers from other countries and from multinational efforts. However, current international investments in productivity-enhancing R&D seem too small to fill the vacuum being created by the changes in developed country research agendas. Who, then, will do the R&D required to generate sustenance for a growing world population when, at least for another century, virtually all the population growth will occur in the poorer parts of the world?

Diverging Research Agendas

During the 1900s, the world's agricultural economy was transformed remarkably, fuelled by agricultural productivity growth, primarily generated by agricultural R&D that was financed and conducted by a small group of developed countries, especially the United States (US), but also France, Germany, and Japan. In an increasingly interdependent world, both developed and developing countries have been dependent on agricultural R&D conducted in the private and public laboratories of

these few countries, even though they have not contributed to financing the activity.

However, dietary patterns and other priorities change as incomes increase. As a result, developed country research agendas are shifting; in particular, the past emphasis on simple productivity enhancement and enhancing the production of staple foods is declining in favour of interest in enhancing certain attributes of food (such as increasing demand for processed and so-called functional foods) and food production systems (such as organic farming, humane livestock production systems, localised food sources and 'fair trade' coffee). In contrast, food security concerns are still pervasive among less affluent communities, predominantly in developing countries.

In addition, to growing differences in consumer demand for innovation between developed and developing countries, R&D agendas may diverge because of differences in producer and processor demands. Farmers in developed countries are demanding high technology inputs that often are not as relevant for subsistence agriculture (such as precision farming technology or other capital-intensive methods). Agribusiness in developed countries is demanding value-adding processes designed to meet consumer demands, and farm production technologies designed to satisfy evolving demands for farm products with specific attributes such as particular food, feed, energy, medical, or industrial applications.

As developed countries' agricultural R&D programs respond to these changing patterns of demand for innovations, the emphasis of the science is being skewed in ways that could undermine the international spillovers that have traditionally contributed significantly to gains in food production throughout developing countries of the world. These spillovers are not generally well understood and their importance is under-appreciated.

Other aspects of agricultural science policy, and the context in which it is conducted, are changing as well. In particular, the rise of modern biotechnology and enhanced intellectual property rights (IPRs) regimes mean that the types of technologies that were once freely available will be more difficult to access in the future. Moreover, the new technologies may not be as portable as in the past. Biotech companies are mostly located in developed countries, particularly in the US, and tend to emphasize technologies that are locally applicable. These and other factors limit incentives for companies to develop technologies for less-developed

countries. Hence some fear less-developed countries may become technological orphans, abandoned by their former private- and public-sector benefactors in developed countries.

New Pressures for Self-Reliance

International spillovers of public agricultural R&D results are extremely important as they have profound implications for the distribution of R&D benefits between consumers and producers, and thus among countries (Alston, 2002). They have also contributed to a global underinvestment in agricultural R&D, which the existing public policies have only partly succeeded in correcting. The stakes are high because the benefits from agricultural technology spillovers are worth many times more than the investments that give rise to them.

The world's least affluent countries have depended on spillovers of technologies from industrialised countries (especially from the US, but also the United Kingdom, France, and others), both individually and through their collective action via the Consultative Group on International Agricultural Research (CGIAR). Until recently, much of the successful innovative effort in most developing countries was applied at the very last stage of the process, selecting and adapting varieties for local conditions using breeding lines and other materials developed elsewhere. Only a few larger countries, such as Brazil, China, and India, were able to achieve much by themselves at the more upstream stages of the research and innovation process, even for improved crop technologies for which conventional breeding methods are widely applied. Until recently, that strategy of conducting adaptive research and relying on spillovers for basic material was reasonable, given an abundant and freely accessible supply of suitable materials; at least for the main temperate-zone food crops.

Changes in the emphasis of developed country agricultural R&D, combined with new IP rules and practices in conjunction with an increased use of modern biotechnology methods, have already begun to spell a decline in the public pool of new varieties. In addition, the other main source of varietal materials, the CGIAR, has changed its emphasis and is scaling back its role of providing finished material or advanced breeding lines. The reduction in spillovers from these traditional sources will mean

that less-developed countries will have to find new ways of meeting their demands for new varieties.

Pervasive Underinvestment

Although investment in agricultural R&D has high returns and has played a major role in helping to provide food for large and expanding populations, support for this form of R&D is declining. Underfunding of agricultural R&D is pervasive, especially in developing counties. This trend is alarming given:

- The continuing and substantive growth of populations, especially in developing countries.
- An increasingly scarce and deteriorating natural resource base.
- The pervasive pockets of hunger and poverty that persist in developing countries, in many cases despite impressive national average productivity increases.
- The growing divergence between developed country research agendas and the priorities of developing countries.

The problem of underfunding may worsen, especially for R&D that is related to the production of food staples in less-developed countries, as evidenced by the recent funding trends.

Public Research Investments

Worldwide public investment in agricultural R&D increased by 51 per cent in inflation-adjusted terms between 1981 and 2000 from an estimated $15.2 billion to $23 billion in 2000 international dollars. During the 1990s, for the first time, developing countries as a group provided more of the world's public agricultural R&D than developed countries did.

The Asia and Pacific region has continued to gain ground, accounting for an ever-larger share of the developing country total since 1981. In 2000, just two countries from this region, China and India, accounted for 39.1 per cent of developing country expenditure on agricultural R&D,

a substantial increase from their 22.9 per cent combined share in 1981. In stark contrast, sub-Saharan Africa continued to lose market share, falling from a 17.3 to 11.4 per cent share of the developing country R&D investment total between 1981 and 2000 (Pardey et al., 2006a).

Paralleling spending patterns for all the sciences, agricultural R&D has become increasingly concentrated in a handful of countries. Just four countries (the US, Japan, France, and Germany) accounted for 66 per cent of the public R&D conducted by developed countries in 2000; about the same as two decades before. Similarly, just five developing countries (China, India, Brazil, Thailand and South Africa) undertook 53.3 per cent of the developing countries' public agricultural R&D in 2000, up from 40 per cent in 1981. Meanwhile, in 2000, a total of 80 countries with a combined population of approximately 625 million people conducted only 6.3 per cent of total agricultural R&D (Pardey et al., 2006a).

The patterns of spending growth are uneven. Certainly, the more recent rates of increase in inflation-adjusted spending for all developing regions of the world failed to match the rapid ramping up of public agricultural R&D spending that Pardey & Beintema (2001) reported for the 1970s. The growth in spending for the Asia and Pacific region as a whole rebounded in the late 1990s from the slower growth rates observed for the 1980s. This was especially so in China and India during the 1996 to 2000 period, in both instances reflecting government policies to revitalize public R&D and improve its commercialization prospects, including linkages with the private sector. Spending growth throughout the Latin American region as a whole was more robust during the 1990s than the 1980s, although the recovery was more fragile and less certain for some countries in the region (such as Brazil, where spending contracted at the close of the 1990s).

Overall investments in agricultural R&D in sub-Saharan Africa failed to grow by more than one per cent per annum during the 1990s, the continuation of a longer-term slowdown (Beintema & Stads, 2004). Even more concerning is the fact that approximately 50 per cent of the 27 African countries for which national total estimates are available, spent less on agricultural R&D in 2000 than in 1991 (Beintema & Stads, 2004).

A notable feature of the trends was the contraction in support for public agricultural R&D among developed countries. While spending in the US increased in the latter half of the 1990s, public R&D was massively reduced in Japan (and also, to a lesser degree, in several European countries) towards

the end of the 1990s, leading to a decline in developed country spending as a whole for the decade. The more recent data reinforce the longer-term trends observed earlier. Namely a fairly widespread scaling back, or at best a slowing down of support for publicly performed agricultural R&D among developed countries is occurring. In part, this points to a shifting emphasis from public to privately performed agricultural R&D, but also to a shift in government spending priorities.

Inevitably, this will affect productivity prospects in agriculture for the countries in question. Pardey et al. (2006b) suggest a more subtle and arguably more important consequence is that a slowdown or cutback in developed country spending will curtail the future spillover of ideas and new technologies from developed and developing countries. Developed-developing country linkages will be even more attenuated as the funding trends proceed in parallel with other policy and market developments. These include strengthening IPRs and biosafety regulations, and a reorientation of developed country R&D agendas away from productivity gains in food staples towards concerns for the environmental effects of agriculture and food quality, as well as the medical, energy, and industrial applications of agricultural commodities. With developed countries as a group still accounting for 44 per cent of public agricultural R&D worldwide (and nearly 80 per cent of all science spending) the consequences of a continuation of these funding, policy, and market trends is likely to be particularly pronounced in terms of the productivity-enhancing effects on food staples.

In addition to these broad trends, other aspects of agricultural R&D funding that have important practical consequences are also of concern. For example, undue variability in R&D funding continues to be problematic for many developing country research agencies. This is especially troubling for agricultural R&D given the long gestation period for new crop varieties and livestock breeds, and the desirability of long-term employment assurances for scientists and other staff (Pardey et al., 2006b). Variability encourages an over-emphasis on short-term projects or on projects with short lags between investment and outcomes, and adoption. It also discourages specialization of scientists and other resources in areas of work where sustained funding may be uncertain, even when these areas have high pay-off potentials.

Public Agricultural R&D Intensities

Turning now from absolute to relative measures of R&D investments, developed countries as a group spent $2.36 on public agricultural R&D for every $100 of agricultural output in 2000: a sizable increase over the $1.41 spent per $100 of output two decades earlier, but slightly down from the 1991 estimate of $2.38. This longer-term rise in R&D intensity in developed countries starkly contrasts with the group of developing countries where there was no measurable growth in the intensity of agricultural R&D (i.e. agricultural R&D spending expressed as a percentage of agricultural gross domestic product, AgGDP). In 2000, developing countries spent just $0.53 on agricultural R&D for every $100 of agricultural output.

At first glance the rise in developed country intensity ratios and the stagnating R&D intensities for developing countries appears to misrepresent the trends in spending, which showed that the growth in investments in agricultural R&D in developing countries significantly outpaced the corresponding growth in investments in agricultural R&D in developed countries (i.e., 3.13 per cent vs. 2.11 per cent per annum from 1981-2000). Delving deeper, agricultural output grew much faster in aggregate for developing versus developed countries over the previous several decades, so that the faster growth in aggregate agricultural R&D spending among developing countries had, nonetheless, barely kept pace with the corresponding growth in output. In addition, more than half of the developed countries, for which data were available, had higher R&D intensity ratios in 2000 than 1981. The majority spent in excess of $2.50 on public agricultural R&D for every $100 of AgGDP. Only 10 of the 26 countries in sub-Saharan Africa in the sample had higher intensity ratios in 2000 than in 1981, while most countries in the Asian and Latin American sample increased their intensity ratios from 1981 to 2000 (nine out 11 Asian countries and eight out of 11 Latin American countries).

Other research intensity ratios are also revealing. Developed countries spent $692 per agricultural worker in 2000; more than double the corresponding 1981 ratio while developing countries spent just $10 per agricultural worker in 2000, an increase of less than 50 percent over the 1981 figure. These developed-developing country differences are, perhaps, not too surprising. A much smaller share of the developed country workforce was employed in agriculture, and the absolute number

of agricultural workers declined more rapidly in developed countries than it did in the developing ones.

While only some segments of society are directly involved in agriculture as producers, everyone consumes agricultural outputs, therefore agricultural R&D spending per capita is instructive. These new data signalled a break with earlier trends. For developed countries, spending per capita rose substantially from 1981 to 1991 (a continuation of earlier trends documented by Pardey & Beintema 2001), but declined thereafter so that spending per capita in 2000 had slipped well below 1991 levels. This developed country reversal was driven mainly by developments in Japan, although only half the developed countries continued to increase their per capita spending on agricultural R&D throughout the 1990s.

Per capita spending rates were much lower among developing compared with developed countries: typically less than $3 per capita for developing countries (especially those in Africa) whereas 59 per cent of the developed countries invested more than $10 per capita in 2000. Nonetheless, and in contrast to the group of developed countries, spending per capita for the group of developing countries continued to rise; from $2.09 per capita in 1981 to $2.72 in 2000. The outliers to this general trend are sub-Saharan Africa, where agricultural R&D spending per capita has continued to decline since 1981, and Latin America, where spending per capita declined from $5.43 in 1981 to $4.94 in 1991, and $4.96 in 2000.

Private Agricultural R&D Investment

In agriculture, in particular, it is difficult for individuals to fully appropriate the returns from their R&D investments, and it is widely held that some government action is warranted to ensure an adequate investment in R&D (Pardey et al., 2006b). The private sector has continued to emphasise inventions that are amenable to various IP protection options such as patents, and more recently, plant breeders' rights and other forms of IP protection. Private investments in agricultural R&D, similar to investments in all forms of R&D, are motivated and sustained by the returns to innovation reaped from the investment. IP policies and practices are but one dimension of the incentive to innovate. Potential market size and the cost of servicing the market, which in turn are dependent on the state of

communication and transportation infrastructure, farm structure and size, and farm income, are important dimensions as well. So too is the pattern of food consumption. As incomes rise, a larger share of food expenditure goes to food processing, convenience and other attributes of food, areas where significant shares of private agricultural R&D effort are directed.

The private sector has a large presence in agricultural R&D, but with dramatic differences between developed and developing countries and among countries. In 2000, the global total spending on agricultural R&D (including pre-, on-, and post-farm oriented R&D) was $36.5 billion. Approximately 37 per cent was conducted by private firms and the remaining 63 per cent by public agencies. Notably, nearly 94 per cent of that private R&D was performed in developed counties, where some 55 per cent of the agricultural R&D was private. In developing countries, only six per cent of the agricultural R&D was private, and there were large disparities in the private share among regions of the developing world. In the Asia and Pacific region, around eight per cent of the agricultural R&D was private, compared with only two per cent of the R&D throughout sub-Saharan Africa. The majority of private R&D in sub-Saharan Africa was oriented to crop-improvement research, often (but not always) dealing with export crops such as cotton in Zambia and Madagascar and sugarcane in Sudan and Uganda. Almost two thirds of the private R&D performed throughout the whole region was carried out in South Africa.

The private share of agricultural R&D spending in Organisation for Economic Cooperation and Development (OECD) countries grew steadily from nearly 44 per cent in 1981 to over 55 per cent in 2000. These increasing private shares reflected increasing industry R&D by the farm-input supply and, especially, the food processing sectors. Around the general trend was much country-specific variation. In the US the private share inched up from 50.1 per cent (compared with an OECD average of 43.9 per cent) in 1981 to 54.3 per cent by 1991, and changed little thereafter. According to these data, Japan conducted slightly more of its agricultural R&D in the private sector than the US. The private share of Australian agricultural R&D has also grown from a small base of 5.9 per cent in 1981 to 20.2 per cent in 1991, then more slowly during the next decade to 23.5 per cent of the total in 2000.

Table 1. Private sector share of total agricultural R&D: 1981-2000.

	1981	1991	2000
	(*percentage*)		
Australia	5.9	20.2	23.5
Japan	36.6	48.4	58.6
US	50.1	54.3	54.6
Other (19)	45.7	48.5	56.9
Total (22)	43.9	49.6	55.2

Source: Compiled by authors from data reported at www.asti.cgiar.org.

Policy Implications

Agricultural R&D is at a crossroads. The close of the 20th century marked changes in policy contexts, fundamental shifts in the scientific basis for agricultural R&D, and shifting funding patterns for agricultural R&D in developed countries. These changes imply a requirement for both rethinking of national policies and reconsidering multinational approaches to determine the types of activities to conduct through the CGIAR and similar institutions and how these activities should be organised and financed. Even though there is no evidence to suggest that the world can afford to reduce its rate of investment in agricultural R&D and there is every indication that more should be invested, it cannot be assumed that developed countries will play the same role as in the past. In particular, countries that in the past relied on technological spillovers 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:

1. The types of technologies being developed in the developed countries may no longer be as readily applicable to less-developed countries as they were in the past.
2. Those technologies that are applicable may not be as readily accessible because of IP protection of privately owned technologies.

3. Those technologies that are applicable and available are likely to require more substantial local development and adaptation, calling for more sophisticated and more extensive forms of scientific R&D than in the past.

In short, different approaches may have to be devised to make it possible for countries to achieve equivalent access and tap into technological potential generated by other countries, and in many instances countries may have to extend their own agricultural R&D efforts farther upstream, to more fundamental areas of the science.

Conclusion

The balance of global agricultural R&D investments is shifting in ways that will have important long-term consequences, especially for the world's least affluent countries. The primary reason is changes in supply and demand for agricultural technologies in developed countries, which have been the main producers of agricultural technologies. These countries seem unlikely to provide the quantities of productivity-enhancing technologies, suitable for adaptation and adoption in food deficit countries, that they did in the past. This trend has been compounded by a scaling back of developed country support for the international agricultural R&D system, which has already diverted its own attention away from finished productivity-enhancing technologies, especially for staple food crops.

A shift in R&D agendas is forcing a rethinking of some national and multinational policies. National Governments can take some initiatives in national agricultural R&D policy, such as: enhancing IP and tailoring the institutional and policy details of IPRs to best fit local circumstances; increasing the total amount of government funding for their national agricultural R&D systems; introducing institutional arrangements and incentives for private and joint public-private funding; and improving the processes by which agricultural R&D resources are administered and allocated.

References

1. Alston, J. 2002, Spillovers, Australian Journal of Agricultural and Resource Economics, vol. 46, iss. 3, pp. 315–46.
2. Beintema, N. & Stads, G., 2004, Investing in Sub-Saharan African agricultural research: Recent trends. 2020 Africa Conference Brief No. 8. Washington DC: International Food Policy Research Institute.
3. Pardey, P. & Beintema, N., 2001, Slow magic: Agricultural R&D a century after Mendel. IFPRI Food Policy Report. Washington, DC: International Food Policy Research Institute.
4. Pardey, P., Beintema N., Dehmer, S. & Wood, S., 2006, Agriculture research and development: A growing global divide? University of Minnesota and International Food Policy Research Institute: St Paul and Washington, DC (in preparation).
5. Pardey, P., Alston, J. & Piggott, R., 2006b, Agricultural R&D in the developing world: Too little, too late? Washington DC: International Food Policy Research Institute.

Note

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Lessons From the Global Environment Facility

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Introduction

The Global Environment Facility, formally established in 1994, helps developing countries and emerging economies fund environmental activities that benefit the global community by:

- Alleviating the effects of climate change through energy efficiency and renewable energy projects aimed at reducing emissions of greenhouse gases.
- Conserving biodiversity through protecting ecosystems and species.
- Working to reduce environmental threats to regional water bodies.

Other areas covered by the GEF include persistent organic pollutants (POPs), land degradation and multi-focal activities.

The GEF is the largest single source of funding aimed at protecting the global environment. So far it has allocated more than US$5 billion for over 1500 projects in 140 countries. For each dollar invested by the GEF, an additional US$3 is provided by partners.

The responsibility for implementing GEF-assisted activities rests with three agencies: the United Nations Development Programme (UNDP), the

United Nations Environment Programme (UNEP) and the World Bank. More recently, a set of executing agencies has been added, but these have completed few projects to date and were not included in the study discussed here. National governments are the main players in implementing most projects in the field, and more than 700 non-governmental organizations have also participated.

The GEF Evaluation Office assesses GEF projects and programs. This chapter presents some of the findings of a major study conducted by the office and published in 2006, *The Role of Local Benefits in Global Environmental Programs*, which focused on the links between global environmental and local benefits in GEF activities. It examined more than 200 projects, including 18 documented in detailed field case studies (GEF Evaluation Office, 2006).

The Scientific Base of GEF Activities

GEF-financed programs and projects centering on environmental protection are developed and implemented on the basis of scientific best practice. The GEF Secretariat, along with its implementing agencies UNEP, UNDP and the World Bank, have substantial technical expertise in the Fund's focal areas of climate change, biodiversity and international waters, which they use in preparing, reviewing, approving and managing GEF activities.

A science and technology panel that advises on strategy and programmes and is supported by a secretariat based at the Washington DC UNEP office also supports the GEF. Known as STAP, its 15 members are internationally recognized experts in the GEF's key areas of work: biodiversity, biosafety, climate change, coastal and fresh water management, sustainable land management, persistent organic pollutants and integrated ecosystem management. The panel also maintains a roster of experts who advise on individual projects.

STAP's objectives are:

- To identify and provide strategic advice on scientific and technical priorities, the coherence of GEF operational programmes and strategies, and emerging issues and gaps relevant to the implementation of operational programmes.

- To provide advice aimed at strengthening the scientific and technical quality and underpinnings of GEF projects.
- To enhance and improve collaborations with other scientific and technical bodies, communities and the private sector in areas of relevance to GEF priorities.
- To advise on capacity building efforts in science and technology relevant to the development and implementation of GEF projects; targeted research relevant to GEF strategic priorities; and monitoring and evaluation indicators for focal areas and cross-cutting issues.

While the GEF's base of international scientific expertise is clearly strong, its record for engaging with experts at national and regional levels is patchier, according to the Fund's own second overall performance study. According to that study, the GEF has involved national scientific communities in preparing reports to conventions, in particular national inventories and national strategies and action plans; but its success at involving developing countries' science and technology communities in designing and implementing country-driven GEF projects sustainably has been 'limited and unsystematic'.

The situation begs two important questions. What happens when science meets society in different locations? And do the scientifically planned changes actually happen — and if so, can they be sustained? The study of local benefits provides many examples of how achievement may be promoted or hindered by factors, most notably social, not included in the 'scientific' approach.

Problems with the Scientific Approach

In projects examined by the GEF Evaluation Office in its *Role of Local Benefits in Global Environmental Programmes*, several factors impeding the successful implementation of scientifically based approaches to conservation have emerged. These are as follows.

Failure to pay enough attention to stakeholders

Many of the projects failed to include any assessment identifying differences within local communities in resource access and use, or in gender, ethnic group and level of poverty, and to develop strategies appropriate to them. Less than a quarter of all project documents referred to any aspect of social analysis at the design stage. In just 14 per cent of the projects, the documents included a reference to a full social assessment, while a further nine per cent referred to other forms of social analysis.

At the implementation stage, there was greater emphasis on aspects of social analyses in 51 of the projects (39 per cent), and a further 4.5 per cent also carried out social assessment. Evaluations, however, rarely included social analyses.

The lack of analysis during the design and preparatory stages of projects contributed to the Evaluation Office's finding that project components intended to generate community-level incentives did not fully reflect the reality of local livelihoods. Without a design process based on an understanding of the dynamics of local social structures and livelihoods, attempts to integrate activities to enhance livelihoods in a locally relevant way were often ineffective.

Even where projects did include social analysis, this was hampered by a number of weaknesses. Social assessment components were often treated as add-on activities rather than essential building blocks, to be interlinked with and inform the design of other components. Other problems included a lack of specified methods and components, unclear objectives and focus, and a poor analysis of policies that may affect attempts to foster local community involvement in resource management. Reviews of some projects revealed a lack of design guidelines or standards for local development aspects.

There have, however, been some signs of improvement: of 30 new projects reviewed by the study, 24 included some level of social analysis in their design. The challenge now is to build on the inclusion of these dimensions in project design, and to ensure that local social dynamics are more effectively incorporated into implementation.

Misunderstanding local natural resource use

Different stakeholder groups were found to have structurally different patterns of needs in relation to the natural resources targeted by the projects. For instance, women, indigenous peoples and the poor were often more dependent on harvesting foods and fuels and accessing natural resources for their livelihoods. Better-off sections of the community were more interested in the commercial exploitation of these resources or in converting common lands for private productive purposes.

Scant regard for indigenous knowledge and conservation practices

Some projects failed to take advantage of local knowledge and values, or were not based on an informed assessment of the long-term sustainability, social organization and environmental impacts of natural resource use by local communities and by people outside them. They thus missed the opportunity to tap into the potential of traditional patterns of ecosystem management by local communities, or explore the extent to which these could be blended with scientific knowledge, to provide a basis for effective and sustainable conservation of threatened ecosystems.

Duplicating the roles of existing local institutions

Community institutions are an important resource, but these projects did not always take advantage of what they had to offer. Where there was engagement with local communities, the approach often aimed to organize new institutions along lines defined by outsiders. In some cases these closely followed existing forms of organization understood by local people, and were effective. But on the whole, forming new organizations often means long delays, considerable costs and problems with sustainability once the project has been completed.

Existing institutions may also be problematic as project instruments — for example, where they are dominated by powerful interest groups and exclude key stakeholders such as minority livelihood groups and, especially, women. Such inequalities can sometimes be overcome through capacity building to improve their inclusiveness and effectiveness. If this is not possible, new institutions may be needed, but the starting point should be to see what is already there (GEF, 2006).

Supportive Policies and Legislation at National and Local Levels

Good practice elements which have promoted effective and sustainable results include:

- Detailed analysis of existing policies and legislation, highlighting areas where these need to be strengthened to help in attaining and sustaining the desired changes in behaviour towards the environment.
- Implementation of programmes to support and develop government ownership and political will towards positive environmental management as well as the capacity and resources to deliver.
- Building realistic timelines into the project for changes and contingency plans in case its objectives aren't reached during the project's lifetime.
- Ensuring there is a programme of action related to national policy and strategic measures, to assist in facilitating the intended local changes.
- Adopting long-term strategies through programmes or collaborations with local institutions, which will have a sustained presence in the country and project localities to ensure that a commitment to better approaches to natural resource management continues.
- Addressing national policies in other sectors to assure that they remain in synch with environmental policies.

Encouraging community co-management of protected areas

In the study, co-management of projects and conservation areas by both communities and the role and boundaries of partnerships differed from project to project and were context driven. In some places, for example, co-management served as a conflict or threat management mechanism, involving the local community in boundary negotiation and policing. In others, it appeared to be strongly associated with efforts to secure sustainable resource use agreements.

Institutional mechanisms were fundamental to co-management. Projects chose between the following approaches, depending on the national and local context:

- Developing new community institutions to address conservation and development concerns within the context of the management of protected areas. This approach has been useful when appropriate local government institutions are lacking, or when the project has been piloting or testing co-management to inform policy development.
- Utilizing existing local government institutions and through this taking advantage of decentralization to exploit opportunities for local co-management.

The main gains from co-management arrangements have been reducing the illegal use of resources, such as poaching, in protected areas, and legalizing and developing access and use agreements for resources such as timber, water, medicinal plants, honey and handicraft materials to provide communities with incentives encouraging conservation. Co-management is also being seen in the formation of 'community conserved' areas in marine, forest and semi-arid regions, set up to improve the management of resources.

Effective capacity building for local institutions

Good practices include:

- Basing capacity building on local needs and tailoring it to project objectives. The temptation to utilize existing programs that are not specifically relevant should be avoided.
- Developing approaches that can blend the most effective elements of traditional knowledge and values with those derived from external science and conservation experience.
- Ensuring that training components, including field trips, are tailored to the needs, experience and institutional location of participants.
- Carefully selecting participants to ensure they have the capacity and intention to engage in natural resource management activities.
- Clearly linking capacity building with the generation of livelihood benefits at individual and community level, either directly through

employment in project-related activities, or through other appropriate income-generating activities.
- Aiming to produce institutions that can sustain the intended project benefits in the long term, whether these are enhanced existing bodies or newly created institutions.

Engaging with communities

The elements of such approaches include:

- Understanding differences within the community, rather than assuming that all members share a common understanding and interests with regard to the environment.
- Developing an approach that treats community members as active partners, with their own beliefs, viewpoints and knowledge, rather than as recipients of externally generated wisdom and instructions.
- Changing project procedures to reflect inputs from the community, rather than consulting the community about a preconceived approach.
- Engaging communities so they actively participate in the selection, design and implementation of any major improvements or other inputs.
- Encouraging appropriate inputs of time and labour from the community to foster a sense of ownership regarding any new community assets.
- Ensuring that the approach to participation is transparent and accountable and that it manages to include a broad spectrum of people, including women, the poor, indigenous peoples and other vulnerable groups.
- Making sure there is enough expertise and resources available to make any community participation as effective as possible.
- Providing adequate support and capacity building so people and institutions can participate fully and effectively as the project progresses.

- Carefully monitoring and influencing approaches to participation of local government and nongovernmental partners to ensure that these conform to those of the project concept.
- Including participation as a topic in monitoring and evaluation systems and in project management and supervision.

Involving specialist skills

An over-concentration on technical" and "scientific skills can crowd out a broad range of other, equally valuable specialist skills. Close teamwork between social and environmental specialists can help establish and develop appropriate areas for building practical bridges between local and external knowledge and strategies for environmental management.

Overall, the GEF and its implementing agencies have placed great emphasis on the importance of a scientifically sound approach to protecting the global environment. In this respect, they have had considerable success and have advanced innovative approaches. However, broader development skills have not been applied at the same level. As a result, some interventions have not achieved their full potential because not enough attention has been paid to social and economic factors in conservation.

Conclusion

As an institution, the GEF serves a number of global environmental conventions and operates from a strong base of scientific best practice. Its project proposals are assessed to ensure they are up to date regarding effective environmental management. But as we have seen, social factors have proven something of a sticking point in some projects during the design and implementation stages.

To ensure that GEF projects are as effective as possible, several approaches — based on a detailed understanding of and engagement with local stakeholders — were found to reduce or remove the limiting effects of social challenges to scientific environmental protection. These findings present a number of broad lessons, suggesting that the introduction of science-based projects is most likely to succeed when based on:

- A detailed understanding of the social and institutional context of the project.
- A willingness to accept that a scientific approach incorporates knowledge and values that may not be shared.
- An appreciation of and collaboration with local people, knowledge, values and institutions.
- Participatory approaches, which give local people a role in the design and management of the projects that affect them.
- Equitable distribution of the costs and benefits of interventions.

References

1. GEF. The second overall performance study (OPS2). GEF, Washington DC.
2. GEF Evaluation Office. 2006. The role of local benefits in global environmental programs. Evaluation Report No. 30. GEF, Washington DC.
3. United Nations Environment Programme Division of Global Environment Facility Coordination. STAP — the Scientific and Technical Advisory Panel of the Global Environment Facility. UNEP DGEF. Available at http://dgef.unep.org/About_GEF/STAP.

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Frameworks for Action: Success Stories in European Union Research Collaboration

Alfredo Aguilar and Sohail Luka

Introduction

The European Research Area, launched in 2000, is a project aiming to overcome fragmentation in European research and innovation. One of the ERA's main objectives was to open up research from the European Union to the rest of the world, and in this it has succeeded. It has enabled countries both within the EU and outside it to participate in joint projects in science and technology, while contributing to knowledge that might improve quality of life in both their regions. More, these collaborations have acted as a catalyst contributing to closer political and economic relations.

So the establishment of ERA in the 6th Framework Programme for Research, Technological Development and Demonstration (FP6) (2002-2006) has been a key milestone in the history of EU research. But it was not the first. EU activities focusing on international scientific cooperation go back as far as 1983, when the Science and Technology for Development Programmes (STD1, 2, 3), which focused on health and agriculture, were launched.

During the next decade, the EU's International Scientific Cooperation Programmes (ISC) were set up in countries in Latin America, Asia and the Mediterranean that had economic agreements with the European Community. Out of dialogues on science and technology, centring on a broad range of topics prioritised by these non-EU countries, came many of the S&T bilateral agreements negotiated over the last 10 years.

The 4th Framework Programme (FP4), which ran from 1994 to 1998, saw the launch of the INCO (International Cooperation) programme — in essence, a merging of STD 1-3 and ISC. INCO involved developing countries, industrialized countries outside Europe, nations in the Mediterranean and Central and Eastern Europe, and newly independent states of the former Soviet Union. Its overall objective, however, has been to develop strong, equitable scientific partnerships with developing countries to contribute to their sustainable development. Focusing on health, natural resources, food security, the environment, and the protection and conservation of cultural heritage, INCO has adapted these areas to the needs of each region.

INCO also had a number of broader initiatives. INCO-Copernicus, for instance, had a more strategic approach in FP4 and in FP5, concentrating on cooperation with Russia and the former Soviet states to enhance their research potential and promote restructuring to better meet regional, social, economic and environmental needs. In 2001, for example, INCO-Copernicus dealt with past conflict in the Western Balkan, especially in the health and environmental sectors.

INCO has had other mandates, such as negotiations on S&T agreements with non-EU countries; providing funding for INTAS [1]; and funding the COST secretariat (European Cooperation in Scientific and Technical Research, set up in 1971) and the AVICENNE Cooperation framework between the EU and 12 non-EU Mediterranean member states. By FP5 (1998-2002), INCO (now known as INCO 2) had embraced a new area of developing policy research in developing countries assessing policy options in a period of rapid political and socioeconomic change. It supported as many as 220 research and research coordination contracts in research policy, health, food security and natural resources.

Many of the issues they tackled were of mutual interest to Europe and developing countries. Food security was addressed through genetic characterisation or enhancement of major traditional food crops in

developing countries, animal health and sustainable aquaculture, agriculture under extreme conditions and safe food processing and agro-food chains. The natural resources policy topics ranged from renewable energy, to barriers to private sector participation in water supply and sanitation and other water policy issues, to challenges in the sustainable use of terrestrial ecosystems such as forests and reconciling multiple demands on coastal zones.

And finally, in FP6 (2002-2006), INCO 2's policy-related activities focused on strengthening multilateral coordination as well as on the definition of research priorities.

Framework 6: Getting the Developing World Involved

Architecture of international scientific cooperation

In January 2000, the European Commission launched its initiative to establish the European Research Area (ERA). Its communication about the ERA, *Making a reality of the European Research Area (ERA): guidelines for EU research activities (2002-2006)* stressed that the ERA must be opened up to the rest of the world. Through this process, the EU aimed to make best use of all the international scientific cooperation policies and activities undertaken within the EU, whether at Community level or in individual member states.

As a follow-up, the EC's communication on the international dimension of the ERA set broad guidelines for a new policy on international S&T cooperation within the context of the 6th Framework Programme for Research and Technological Development (FP6) and its launch. This policy fulfilled the strategic objectives of opening up the ERA to the world, which were specifically:

- To help European researchers, businesses and research organizations in the EU and in the countries associated with the FP6 to have access to knowledge and expertise elsewhere in the world.
- To help ensure Europe's strong and coherent participation in the research initiatives conducted at international level in order to push back the boundaries of knowledge and to help resolve major global issues.

FP6 covered science, research and innovation in this context. Launched with a budget of €17.5 billion for 2002 to 2006, its central objective was to contribute to the ERA by improving the integration and coordination of research in Europe. At the same time, that research was targeted at strengthening the competitiveness of the European economy, solving major social questions and supporting the formulation and implementation of other EU policies. According to Article 164 of the Treaty of the EU, the European Community carried out the following activities to complement those carried out by member states:

- Implementing research, technological development and demonstration programmes by promoting cooperation between those programmes, research centres and universities.
- Promoting cooperation in EC research, technological development and demonstration with non-EC countries and international organisations.
- Disseminating results of activities in EC research, technological development and demonstration.
- Stimulating the training and mobility of researchers in the EC.

The FP6 was accordingly divided into three specific programs, one for integrating and strengthening the ERA, one for structuring it, and one for strengthening its foundations.

The majority of non-EU countries in FP6 were so-called INCO (for international cooperation) partner countries, with low or medium per capita incomes. These were further broken down into:

- Developing countries (DEV), subdivided into Africa, Caribbean and Pacific Countries (ACP), Asia and Latin America (LA).
- Mediterranean partner countries (MPC).
- Western Balkan countries (WBC).
- Russia and the New Independent States (NIS).

INCO countries were able to participate in FP6 via three different mechanisms. The first concerned specific measures supporting international cooperation, and covered three primary areas — health, the environment and food security. The second centred on thematic priorities (see Table 1 below), and the third focused on mobility activities under Marie Curie Actions.

Table 1. Schematic overview of the structure of FP6

The 3 headings in the Sixth Framework Programme								
Specific Programme 1 (SP1): Focusing and Integrating the ERA								
7 PRIORITIES THEMATIC AREAS							Specific activities Covering a Wider Field of Research	
Life Sciences, Genomics and biotechnology for health	Information society technologies	Nanotechnologies and nano-sciences, knowledge-based functional materials, new production processes and devices	Aeronautics and space	Food quality and safety	Sustainable development, global change and ecosystems	Citizens and governance in a knowledge-based society	Research for policy support	New and emerging science and technologies (NEST)
							Specific research activities for SMEs	
							Specific international co-operation activities	
Specific Programme 2 (SP 2): Structuring the ERA							Specific Programme 1 (SP1): Strengthening the foundations of ERA	
Research and Innovation	Human resources & mobility	Research infrastructures	Science and society				Co-ordination of research activities	Development of research/innovation policies

Partners in FP6

The observations introduced in this section are based on a statistical analysis of FP6 contracts that were already signed up to 24 January 2006. This roughly corresponds to about 65 per cent of all the calls for the whole duration of FP6. Therefore, while it is not possible to make final conclusions about the participation of INCO countries in FP6 before its conclusion, this data still enables the Commission services to identify some useful trends and can provide helpful "hints" through the initial stages of FP7.

Up to the start of 2006, some 1511 people from INCO target countries had participated in FP6. That figure suggests quite an impact; but to analyse it, two considerations need to be taken into account. One is that while each "participant" is represented by the legal entity that ultimately signs the contract, the actual benefits from these collaborations usually extend to more than one group within that same legal entity. The other is that even with a relatively small financial contribution, an INCO participant in a large project consortium would have access to a disproportionate amount of research know-how, results and infrastructure. Therefore, the projected impact on scientific excellence and capacity in INCO countries is actually much larger that what would appear if looking only at EC contribution figures.

Generally speaking, groups from INCO regions were more active in the first specific program (SP1) than in SP2 and SP3. Only Russia and NIS participated in all FP6 activities. WBC had a relatively high participation in SP2, but no participation in EURATOM. Asia participated moderately in SP2, specifically in Human Resources and Mobility and Science and Society (also in EURATOM, but with no EC contribution). Latin America had a similar participation to Asia, but with no participation in EURATOM. ACP had a much lower participation in SP2 and SP3, while MPC participated only in SP1.

Given the minimum requirements for eligible consortia, and the dedicated budget, it could be argued that within the specific measures of INCO, the participation of groups from INCO target countries was to a great extent protected. Conversely, the Opening has pooled groups from INCO target countries with the rest of the world in the open market of scientific research. So the ability of a region or a country to actively

Table 2. Overall participation of INCO target countries in FP6 [6]

Activity	Number of Contracts	Number of Participations	EC contribution to INCO Participations in million €
INCO actions	204	782	79.5
Thematic Priorities	343	561	59.7
Others activities	100	168	12.4
Sum:		1.511	**151.6**

Table 3. Participation of regions in specific measures in support of international cooperation

INCO-Regions	Number of Contracts	Number of Participations	EC contribution to Participations in million €
MPC	49	205	19.0
ACP	29	125	15.6
ASIA	31	118	15.1
LATIN AMERICA	33	102	13.1
WBC	29	117	9.4
Russia + NIS	33	115	7.3
Sum:		782	**79.5**

participate in the Opening would reflect a solid base in its scientific research community as well as an established level of scientific capacity and infrastructure.

Significant variation was observed as to whether a region was more actively participating in the INCO Specific Measures or in the Opening. A question worth asking here is why some regions failed to participate fully in the Opening. This could be down to a lack of knowledge about this possibility to participate, a lack of capacity to successfully participate, a lack of interest, or a combination of all three. Definite answers will have

to come from further reflection, taking into account the realities of the regions concerned.

As mentioned above, INCO target countries were grouped into six regional clusters. Specific Measures for International Cooperation were specific to these regions, tailoring the research priorities of these to the realities and needs of each region. The participation of each region varied significantly, as Table 3 shows.

Framework Programme 7: Towards 2013

In April 2005, the EC adopted proposals concerning Framework Programme 7 (FP7) for research, technological development and demonstration activities (2007-2013). By 2006 the program had been amended and largely agreed.

FP7 will focus on strengthening industrial competitiveness and meeting the research needs of other EC policies, thereby contributing towards the creation of a knowledge-based society building on the ERA and complementing activities at a national and regional level. It aims to promote excellence in research, technological development and demonstration through the following four programs: cooperation, ideas, people and capacities (see Table 4 for the number of programmes FP7 runs, by subject).

The international dimension

Under the Framework Programmes, any actions promoting international cooperation must show a clearly defined European "added value". Under FP7 that will be the opening of all activities carried out in the thematic areas to researchers and research institutions from all third countries, with restrictions for the theme of security if and where appropriate.

With specific cooperative actions in each thematic area (see Table 4) dedicated to countries outside the EU, in the case of any mutual interest in cooperating on particular topics, these are to be selected on the basis of those countries' scientific and technological level and needs. These actions will be closely associated with existing bilateral cooperation agreements or multilateral dialogues between the EU and the same countries or groups

Table 4. Number of FP7 programs by subject

COOPERATION	**32,292**
Health	5984
Food, Agriculture and Biotechnology	1935
Information and Communication Technologies	9110
Nanosciences, Nanotechnologies, Materials and new Production Technologies	3467
Energy	2265
Environment (including climate change)	1186
Transport (including Aeronautics)	4180
Socio-economic Sciences and the Humanities	607
Security and Space	2858
IDEAS	7460
PEOPLE	4727
CAPACITIES	4291
Research Infrastructures	2008
Research for the Benefit of Small and Medium-Sized Enterprises	1266
Regions of Knowledge	126
Research Potential	350
Science in Society	359
Activities of International Cooperation	182
Non-Nuclear Actions of the Joint Research Centre	1751
TOTAL	50,521

of countries, and will serve as privileged tools for implementing the cooperation between the EU and these countries.

Beyond serving fields of mutual interest, such actions also include those aimed at reinforcing the research capacities of candidate countries as well as neighbourhood countries. They can also include cooperative activities targeted at developing and emerging countries, focusing on their particular needs in fields such as health, agriculture, fisheries and the environment, and implemented in financial conditions adapted to their capacities.

For the people who work in European research and development, a fundamental component of the experience is its international dimension.

Within FP7, this will be addressed through career development for European researchers, and strengthening international cooperation through the actions of researchers. Under the programmethe career development of researchers from member states and associated countries will be supported in two ways. One is through outgoing international fellowships, with a mandatory return, for experienced researchers within a framework of life-long training and competence diversification. The second is through return and international reintegration grants for experienced researchers after a work period abroad. Under this, the networking of researchers from member states and associated countries abroad will also be supported, with a view to keep them actively informed about and involved in developments in the ERA.

For researchers from outside the EC, other support will be provided. One strand is incoming international fellowships, which are designed to attract highly qualified researchers from outside the EC to member states and associated countries to enhance their knowledge and build up high-level connections. Researchers from developing countries or from countries with emerging economies may benefit from support for a return phase. Help with developing contacts and networking in member states for these researchers will also be provided, with a view to structuring and developing contacts within their own regions.

The second strand of help for researchers outside the EC will be the introduction of partnerships between groups of research organisations in Europe and one or more organisations in countries covered by the European Neighbourhood Policy, and those that have an S&T Agreement with the EC.

On the basis of joint programmes, EC support will also be provided for short exchanges of early-stage and experienced researchers to organize mutually beneficial conferences and other events, and to develop a systematic exchange of good practices with a direct bearing on issues to do with human resources in research and development.

To identify and establish areas of research that are mutually important to both EC and targeted non-EC countries for the international cooperation aspects of the specific program on capacities, the focus will be on enhancing ongoing policy dialogues and partnership networks with different regions in the non-EC countries. Coherence of national activities on international scientific cooperation will be enhanced by support for the

coordination of national programmes in member states, EC candidates and associated countries via the multilateral coordination of national RTD policies and activities.

In the FP7, cooperation with non-EC countries will focus on candidate countries; Mediterranean partner countries (MPC), Western Balkans countries (WBC) and the Eastern Europe, Caucasus and Central Asian countries (EECCA); developing countries; and emerging economies.

The main activities for developing jointly agreed international scientific cooperation policies are as follows.

Regional priority setting and defining S&T cooperation policies

EU S&T cooperation to set priorities will be based on comprehensive policy discussions with partner countries and regions, taking into account their socio-cultural conditions and research capacities. This will take place through a number of channels, including international fora (the various UN conventions); Asia-Europe Meetings (ASEM); Latin America, Caribbean and EU (ALCUE); the Mediterranean and Western Balkan Partnerships; the EU-ACP (African, Caribbean and Pacific) States and Eastern Europe, Caucasus & Central Asia; and bilateral and multilateral agreements, as well as informal

The highest priority will be given to strengthening bi-regional/bilateral dialogues to set the framework for international S&T cooperation and joint identification of mutually important research areas. All these initiatives will be implemented through specific international cooperative activities that will develop the bi-regional dialogue in close consultation with member states, associated countries and international cooperation partner countries.

Taken as a whole, these measures will have direct impacts on the enhancement and development of S&T Agreements and S&T Cooperation Partnerships, and a positive synergistic effect on the coordination of national policies and activities on international S&T cooperation.

Within the framework of S&T Agreements, and in accordance with the defined priorities, the identification of new, emerging elements deserving actions will be given priority.

Enhancing and developing S&T cooperation partnerships

To bring the identified priorities to fruition, equitable S&T Cooperation Partnerships will be set up to regroup multiple stakeholders (partners from research, industry, government and civil society) for research capacity building and research actions. These partnerships will need to develop multidisciplinary approaches to tackle diverse needs on a global, regional and/or country level.

The partnerships, based on bi-regional leadership and the coordination of political initiatives in defined priority areas, will be operated by steering groups composed of representatives from each region, open to all partners in the regions concerned, and taking into account their interests and research capacities. They will promote joint research activities and permanent policy dialogue on the efficiency and effectiveness of their cooperative activities, as well as on the identification of future needs.

Coordinating policies and activities on international S&T cooperation

To promote and encourage an effective, efficient international scientific EU cooperation strategy at EU level, continuous coordination of national policies is essential to realise commitments undertaken through the S&T bi-regional and bilateral dialogues.

This coordination will reinforce the efficiency and impact of the ongoing bilateral S&T cooperation initiatives between member states and international cooperation partner countries, and enhance the positive synergies between them. It will also enhance complementarities between EC and member states' S&T cooperation activities. More, it will support the implementation of a shared vision, facilitating innovative approaches and working closely among and with member states in developing and implementing coherent cooperation in EU science and technology.

References

1. INTAS is an International Association for Promotion of Cooperation with scientists from Russia and the NIS. Its activities are described in the website: www.intas.be.

In addition to the payment of the subscription for its membership the European Community has granted financial support to INTAS activities.
2. Towards a European Research Area': COM (2000) 6.
3. Making a reality of the European Research Area: Guidelines for EU research activities (2002-2006)' : COM (2000) 612 final.
4. International dimension of the European Research Area: COM (2001) 346 final.
5. 4 EC Treaty : OJ C 340, 10.11.1997
6. European Commission. 2005. Impact assessment report on the Specific Programme International RTD Cooperation Fifth Framework Programme (1998-2002). European Commission, Brussels, Belgium. EU22019.
7. 2006. Amended proposal for a Decision of the European Parliament and the Council concerning the 7th Framework Programme of the European Community for Research, Technologies Development and Demonstration Activities (2007-2013), Brussels, Belgium. COM(2006)364 final.
8. European Commission. 2005. International scientific cooperation with developing countries: EU-funded research projects (FP5). European Commission, Brussels, Belgium. EUR21113.
9. 2005. Proposal for a regulation of the European Parliament and of Council laying down the rules for the participation of undertakings, research centres in universities in actions under the Seventh Framework Programme and for the dissemination of research results (2007-2013). Brussels, Belgium. COM(2005)705 final.
10. 2006. Amended proposal for a Council Decision concerning the Specific Programme "Cooperation" implementing the Seventh Framework Programme (2007-2013) of the European Community for research, technological development and demonstration activities. Brussels, Belgium. COM(2005)440 final/2.

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Biotechnology Research Parks in Development, Healthcare and Technology-Transfer

Lewis Collens

Introduction

Throughout history, technological advance has spurred on economic development (Solow, 1956), and in the 21st century biotechnology — the application of biological systems and living organisms to produce products and processes — is widely hailed as a new force in the drive towards prosperity. But the potential of biotechnology to improve lives and livelihoods depends on efficient systems of technology transfer between the creators of intellectual property and those best able to develop and exploit new applications.

By its very nature, technology transfer involves collaboration, making biotechnology research parks — which are designed to facilitate partnerships between academic institutions, companies, non-profit organizations and the like — ideal arenas for the process. In essence, these parks are places where pure scientific research can be tested to determine whether ideas are workable, and where marketable products can be developed and financed. Rather than asking the research scientist to become an entrepreneur or the engineer to become a lobbyist, the biotechnology research park brings

the worlds of academia, commerce and government together in mutually beneficial interactions.

This emphasis on partnership is highlighted by the International Association of Science Parks (IASP) in its definition of a research park as an organization "whose main aim is to increase the wealth of its community by promoting the culture of innovation and the competitiveness of its associated businesses and knowledge based institutions" (IASP, 2002). Research parks per se receive significant funding from governmental and private philanthropic sources and provide a broader range of services, including shared research facilities, analytical equipment and animal laboratories, specialized library databases, information technology infrastructure, joint purchasing arrangements, legal services, financial advice and access to venture capital. Of the world's 400-plus research parks, roughly 40 per cent are located in North America, 39 per cent in Europe and 14 per cent in Asia. Most of the world's research parks have at least some biotechnological component — a trend that is on the rise.

Biotechnology research parks are inevitably specialized, covering products and research in agriculture, including genetically modified food and organisms; food processing and safety; bio-computing; and diagnostics, pharmaceuticals and devices in the areas of health and medicine. A look at such parks in developed regions such as North America, Europe and East Asia can be a salutary way of examining the economic returns they generate — and through that, any implications for developing countries thinking of investing in them.

Regions Richest in Research Parks

North America

University research parks are something of an established tradition in North America. More than 200 of them have been built over the past four decades, and their history has been one of tremendous growth. Nearly 83 per cent of them have been incorporated as nonprofit entities, and 69.7 per cent of them were established in the 1980s and 1990s with the help of public funds (AURP, 2003). At the start most of the parks focused on information technology, but in newer parks such as University Technology Park at Illinois Institute of Technology, biotechnology is dominant, while older parks are rapidly switching their overall focus to it.

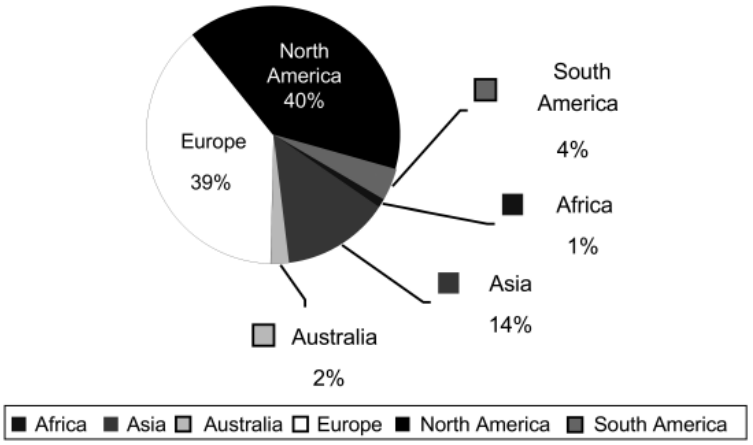

Figure 1. Research Parks by Region (IASP and AURP members)

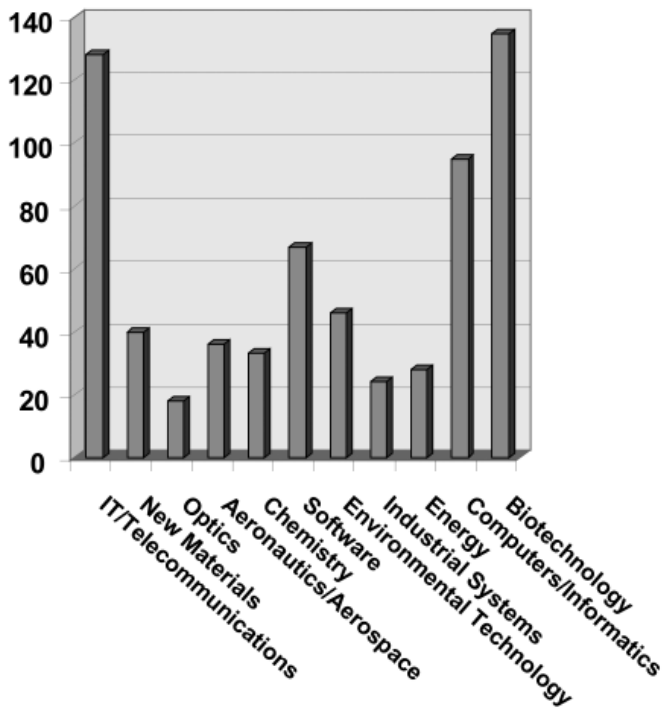

Figure 2. Technologies in Research Parks (IASP)

The Research Triangle Park in North Carolina, one of the oldest and largest research parks, is a case in point. While still dominated by IBM, which has 10,000 employees there, its second largest presence is pharmaceuticals giant GlaxoSmithKline, with around half that number of staff. The park also recently received $150 million to establish a new biotechnology centre. With over 100 research and development organizations and $2.2 billion in capital investment since 1959, the Research Triangle Park continues to exemplify what can be achieved through public/private collaboration.

Thirteen metropolitan areas — Boston, San Francisco, Philadelphia, New York, San Diego, Seattle, Raleigh-Durham, Washington/Baltimore, Los Angeles, Chicago, Detroit, Houston, and St Louis — account for the majority of biotechnology activity in North America, and each conurbation has at least one major university research park. Spin-off companies in North America have been shown to be concentrated in older parks associated with richer university environments, as well as parks geographically closer to their university partner (Link, 2005). Overall, then, the North American research climate is mature, characterized by biotechnology research parks in university settings.

Europe

Europe's quota of research parks nearly equals that of North America, but there is an important difference between the two. Funding for research parks in Europe comes mainly from government, whereas in North America the private sector is the prime source. As a result, the development of research parks in Europe often stems from government programs aimed at reinvigorating local economies through re- industrialization and supporting existing businesses (Bigliardi, 2006), At the same time, investment in biotechnology companies has increased to nearly €2 billion a year (Ernst & Young, 2005). Collaborations between universities and businesses remain central to the research park model in Europe; however, perhaps because higher education is funded primarily by the government, government bureaux invest the most capital in the parks and also manage most of them.

Europe's research environment is a complex and mature one, as the Novum Research Park in Stockholm, Sweden, shows. The park was created by the Stockholm County Council and Karolinska Institute in 1984. Since

then, it has gone on to forge partnerships with Södertörn University College and the medical research group of the Royal Institute of Technology. The collaborations have led to the proposal for an ambitious new project, the Novum Biocity, a complex aimed at providing space for basic research in the biosciences and opportunities to attract more research enterprises.

East Asia

Since the 1990s, China has developed research parks to "redesign the economic architecture" of the country (Sutherland, 2005), and the country's 53 state-level science and technology parks dominate the East Asian scene. However, these cannot be thought of as conventional science parks. China's research parks encourage production, not innovation or technology transfer, and the business environment in China — in particular, the government's control of the central economic policy-producing bodies — is not conducive to fostering international collaborations. Yet science parks are important factors in China's trade output, accounting for US$168 million a year, and it is estimated that half of private R&D is already in the hands of multinational corporations (Van der Osten, 2005).

The Hong Kong Science and Technology Park was developed in 2001 as a hub for technological innovation in electronics, biotechnology, precision engineering, information technology and telecommunications. It currently houses over 120 enterprises and is unique among state-level science parks in China because of its incubator strategy for promoting the establishment of collaborative networks with local universities. The park's emphasis on collaboration between industry and academia is similar to the strategies employed in the West, and encourage technology transfer and business development. But the focus in Hong Kong remains on production rather than research.

Regions Showing Recent Growth

Beyond North America, Europe and East Asia, the rest of the world accounts for just 5 per cent of research parks. But over the past five to 10 years in South Africa, Dubai and Malaysia, there has been significant growth in the conditions that make biotechnology research parks possible.

Key sectors have been working towards the same goal: industry, by creating communities of like-minded businesses; academia, by taking advantage of business opportunities and creating a better climate for technology transfer and for students and faculty; and government, by generating economic development. And now, three significant successes have emerged.

The Innovation Hub is South Africa's first research park. Launched in 2000, the Hub is affiliated with the University of Pretoria, with support from the South African government agency, the Council of Scientific and Industrial Research. The park is an incubator for research enterprises in information and computer technology, biosciences, electronics, and advanced materials and manufacturing.

Neville Commins, CEO of the company managing the Innovation Hub, has said: "It is clear that we are still largely perceived as an adopter, rather than an innovator, of technology. To retain — and enhance — our competitiveness, we must do more to augment the imported…technologies. The imperative is to…spur innovation and exploit intellectual property, so that we can feed the technology commercialization value chain that will ensure revenue generation" (Commins, 2005). And in fact the number of enterprises at the Hub has grown from five to 25 since its inception.

In Dubai, Dubiotech is the centerpiece of the city's economic development strategy. The municipal government has already invested $545 million in capital to attract foreign direct investment in research in the energy and power sectors. The government plans to offer liberal legislation on the use of embryonic stem cells to help researchers look for treatments for diabetes, Parkinson's disease and other pressing health issues. Dubiotech is likely to attract pharmaceutical companies as a result of the government's efforts to create the right balance of liberal bioethical regulation and intellectual property rights (Foreman, 2006). The government's efforts to create a centre of excellence in biotechnology at Dubiotech, while promoting a regulatory environment conducive to the research undertaken there, are unique in the world.

Malaysia's BioValley project is more controversial. Three years ago, the Malaysian government launched this network, aiming to link major research centres and universities with the overall goal of making Malaysia a major player in the global biotechnology arena over the next 10 years (Kandiah, 2003). Under the project there have been efforts to establish biotechnology centres of excellence, build a pool of skilled workers in the

industry, and improve the country's legal and regulatory frameworks so researchers can enjoy financial rewards from their R&D.

But there has been a slow rate of economic return at BioValley, a problem partly caused by the very nature of biotechnological development. According to the Brookings Institution, "It often takes a decade or more to develop biotechnology based products, and perhaps one in 1000 patented biotech innovations produce a successful commercial product" (The Brookings Institution, 2002). Professor Finn Hannsson of the Copenhagen Business School in Denmark suggests that these types of investment may create sufficient social capital that will over time bring a good return.

It is hard to know whether this is the way to assess BioValley. By one measure, a university research park running under capacity is a failed real estate venture, but in the broader view — taking social as well as economic factors into account — university research parks are investments that benefit students and faculty. The benefits over time may be economic, but the short-term benefits will be improved lab space for educational uses and an environment of innovation and entrepreneurship.

New Model in the Making

We've now looked at the mature collaborative research environments of North America, Europe and East Asia, and the emergent settings of Africa, the Middle East and South Asia. Is there a research park agenda for the developing world that we can pull from these examples?

To answer this question we need to look at international trade. There are essentially three tradeable elements: natural resources, labour and intellectual capital. However, a vibrant trading economy presupposes a developed infrastructure. In the 20th century, that meant railroads, highways, electricity and telecommunications. In the 21st century, should research parks be added to that list? If mature collaborative environments — a precondition and condition of the research park — can provide a solution to the problem of brain drain in the developing world, the answer is yes.

The question then becomes how. In the short term, international assistance and other forms of public funding will be required to create

the necessary infrastructure. The European Union continues to announce initiatives to expand research partnerships with developing countries, including financial support. Philanthropic organizations such as the Bill and Melinda Gates Foundation have committed to providing over US$6 billion in global health grants. Multinational corporations like Abbott Laboratories recently financed the creation of a major research center in Tanzania — the largest in sub-Saharan Africa.

On a more grassroots level, many universities are actively engaged in proving assistance in less developed countries. Recently, for example, a team of students from Tec de Monterrey in Mexico collaborated with a team from Illinois Institute of Technology to develop a low-cost water filtration system that will improve human health and create jobs for people in the local community.

Conclusion

Research parks affiliated to universities and government agencies and departments are established mechanisms capable of fostering new ventures and promoting economic development. Wherever they are, the success of such parks depends on the economic, political and social operating environment.

Where some of these forces are working favourably — South Africa, Malaysia and Dubai, for example — new research park ventures may well take root. But long-term economic success must be measured in terms of job creation, improved public health and better access to a quality educational system. The successful research park can improve the human capital of a region through the creation of spin-off companies and the culture of research entrepreneurship that is part and parcel of a vibrant collaborative environment. In countries with serious public health issues, the measure of economic success can be more directly tied to the development of pharmaceuticals and other discoveries to improve public well-being. And finally, improvement in the social operating environment can be measured by the attraction or development and retention of educated knowledge workers.

References

1. AURP. 2003. University Research Park Profile 2003. Association of University Research Parks, Reston, Virginia, p 9.
2. Bigliardi, B. 2006. Assessing science parks' performances: directions from selected Italian case studies. *Technovation*. Vol. 26, p. 493.
3. The Brookings Institution. 2002. Signs of life: the growth of biotechnology centers in the US. Brookings Institution, Washington DC, USA, p 4.
4. Commins, N. 2005. Innovation in South Africa — are we doing enough? Newsbits. Vol. 4, No. 10. Available at: http://www.theinnovationhub.com/newsbits/vol4no10/news02.cfm.
5. Ernst & Young. 2005. 'Ernst & Young's 2005 Global Biotechnology Report'. Antwerp, Belgium, p 4.
6. Foreman, C. 2006. Brave new worlds. Middle East Economic Digest. Vol. 50, No. 6, p 8.
7. IASP International Board. 2002. Definition of Science Park. IASP, Malaga, Spain. Available at: http://www.iasp.ws/information/verdefinicion.php?idnot=3.
8. Kandiah, P. 2003. Hub to boost biotech research. Managing Intellectual Property. Available at: http://www.managingip.com/?page=10&fPUBID=34&ISS=12532&SID=472345&TYPE=20.
9. Link, A. N. and Scott, J. T. 2005. Opening the ivory tower's door: an analysis of the determinants of the formation of US university spin-off companies. Research Policy. Vol. 34, No. 10, pp 1106-1112.
10. Van der Osten, A. 2005 Institutional landscape, legal issues and policy setting, and funding research. Discovery to Delivery: BioVision Alexandria 2004. Bibliotheca Alexandria, Alexandria, Egypt, pp 303-310.
11. Solow, R. M. 1956. A contribution to the theory of economic growth. Quarterly Journal of Economics. Vol. 70, No. 1, pp 65-94.
12. Sutherland, D. 2005. China's science parks: production bases or a tool for institutional reform? Asia Pacific Business Review. Vol. 11, No. 1, pp 83-104.

Infectious diseases, cancer, diabetes, diseases of poverty and malnutrition: the healthcare and food security challenges facing us all can at times seem overwhelming. In many countries and for many people, they are the cause of much loss of life and incalculable suffering.

When it comes to malaria, diarrhea and tuberculosis, the poorest are more likely to be susceptible. But other diseases, such as diabetes and cancers are indiscriminate in whom they target. These are a function of the fact that, though we are living longer, we lead more sedentary lives; smoke and consume a range of diets that would have seemed alien even one generation ago.

The authors of *Changing Lives* are leading researchers and policymakers from both developed and developing countries. Together, they highlight the challenges and the successes in delivering better healthcare and nutrition to those most in need. Working in a unique partnership, they demonstrate the potential that the new life sciences offer for enhanced nutrition, food security and better healthcare for all.

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