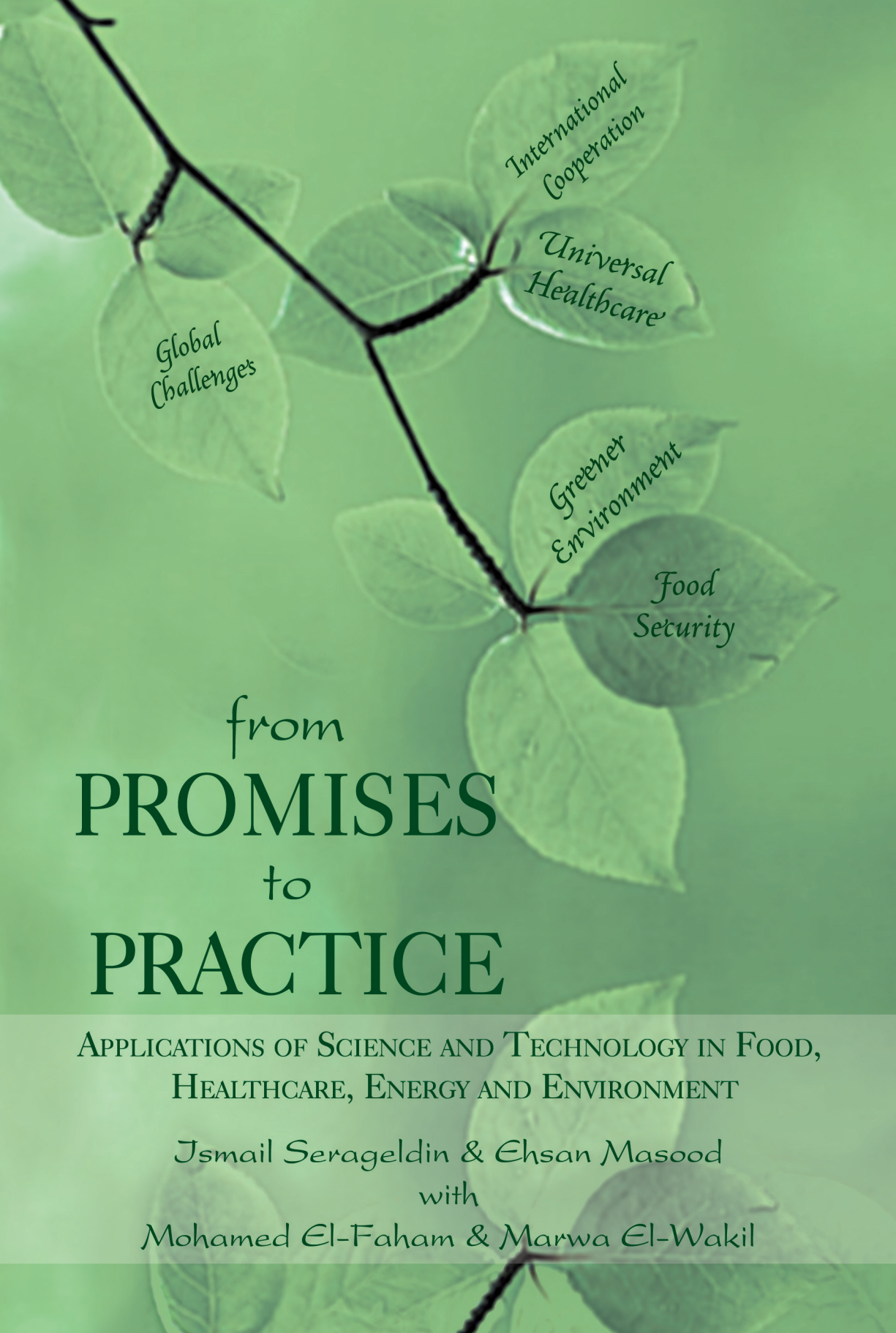

from PROMISES to PRACTICE

Applications of Science and Technology in Food, Healthcare, Energy and Environment

Ismail Serageldin & Ehsan Masood
with
Mohamed El-Faham & Marwa El-Wakil

From Promises to Practice

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BioVisionAlexandria 2008

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Today's Young Are Tomorrow's Leaders

Ismail Serageldin

The topic of BioVisionAlexandria 2008, 'From Promises to Practice', is designed to highlight a fundamental difficulty experienced by almost everyone who lives in the South, in the developing world. When we look at the fruits of science, we cannot but fail to notice that the promises of science mostly benefit those who already have much; and that not enough is being done to address the needs and concerns of the poorest.

So what do we ask? We ask: 'What can science do to help us and what can wise policies do to help us?' Why do I say wise policies, and not just 'good' policies or 'effective' policies ? I use the word 'wise' because there is a lot of talk these days about living in the third global revolution: the information age, the knowledge society. It is true of course that when data is organized it becomes information; and that information when explained becomes knowledge. But we need more than knowledge. We need wisdom: wisdom to craft the sound policies that will ensure that the benefits of science are shared with all.

Three challenges in particular will need all of our collective creativity. The first of these is food. It is no secret that food shortages have led to riots in Mexico and elsewhere. There have been tensions in Egypt too about rising food prices. It is also no secret that governments' ability to step in with ever-increasing subsidies is limited.

Why is this happening now?

There are a number of reasons, some of which have to do with prosperity in parts of the developing world. Those of us who experience higher incomes can afford diets that are richer in proteins. At the same time more of us are getting the keys to vehicles that run on fossil fuels mixed with biofuels. A situation is emerging where food, feed and now fuel are all competing for the same land and the same water. Not just that but the world's appetite for fuel and energy is burning the very food that we all want and need. The net effect is that the price of food, that most basic of all human rights, is increasingly beyond the reach of the world's poor.

The second challenge is what I call 'public health and private medicine'. It is tremendously exciting to see major advances in medicine, and more and more sophisticated techniques for medical treatment. But these are mostly available to those who can pay, or to those whose governments can pay. The world's poorest are being left behind – and would be even more disadvantaged were it not for generosity of private philanthropists such as the Gates Foundation and others. The challenge to provide accessible and affordable healthcare for the peoples of the developing countries is a public need; but so far the best answers seem to be coming from the private sector.

My third challenge is climate change. This is a challenge that faces all of humanity, as we share one single planet. If Earth is in peril, so are we all. Climate change is no discriminator of rich, or poor. Both North and South will feel its effects. Except in one sense: richer countries will be able to face down some of the threats. The poorest countries on the other hand will be least equipped. When the cycles of rain and drought become more frequent; when growing seasons become shorter; when infectious diseases become more prevalent, it will be the South that will be more threatened.

What then is to be done?

There are many interventions that can be done – indeed many excellent examples are described in this volume. But in addition all developing nations must do one thing and do it well if they want to be able to survive these and other challenges. They must strengthen science in their countries. They must invest in education at all levels; and they must invest in R&D.

There is no alternative to the fact that solutions to global challenges will not emerge unless more -- many, many more -- of our talented young people are given an opportunity to excel.

Here at the Bibliotheca Alexandrina, we are playing our part to achieve that end, for example through events such as BioVisionAlexandria where Egypt's young are given access to some of the world's finest minds – such contacts can often be a turning point in the life of a young person. We are playing our part in other ways, such as online learning activities like the Supercourse, which had 8 million people access its pages on our website; and through the fact that the Bibliotheca Alexandrina itself is a nursery for tomorrow's scientific and cultural leaders – our average age is just 30.

A perennial aim of BioVisionAlexandria is to reach across the divide that divides us, to reach out, shake hands and work together in partnerships that would enable us not only to strengthen science in the developing countries but also to construct and strengthen bridges of collaboration and cooperation. For it is only through genuine cooperation and trust will we emerge from the many threats we face today to build a better tomorrow.

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Foreword

Ahmed Nazif, Prime Minister of Egypt

BioVisionAlexandria represents a unique forum for scientists, experts, and other stakeholders to share thoughts, theories, best practices, and experience of scientific progress and human knowledge. It is imperative that the immense advances taking place in science must lead to significant and noticeable improvements in the lives of the poorest.

FIRST WORDS

We Need a new Solidarity

Philippe Desmarescaux

It is now clear and widely accepted that many factors are challenging our most basic models and notions of economics, society and international relations, as well as our way of life.

Be it globalization, which affects every sector of activity and every country. Be it population, which continues to grow and is increasingly concentrated in sprawling mega-cities, creating a whole new range of problems. Be it climate change. Be it the finite amount of natural resources (energy, water, raw materials, land and so on) which cannot meet our growing needs. Be it the rising insecurity made worse by fanaticism, desperation and alarmingly efficient and accessible means of destruction.

Thankfully, in the face of these many challenges, new concepts, proven innovations and successful experiences give us hope that we can overcome these obstacles. New opportunities at the interface of science and technology will allow us to roll out new, more efficient and more affordable solutions.

At the interface of the life sciences and nanotechnologies, more precise diagnostic tests and better targeted treatments will make it possible to fundamentally change our health care systems.

At the interface of neurosciences and information technology, new tools using artificial intelligence will facilitate the development of the innovations we need.

Successful cooperation between the public and private sector, between national, international and non-governmental organizations open up possibilities for new and more efficient ways of working together.

Growing levels of funding contributed by individuals and foundations, which sometimes exceed the existing resources of countries or international organizations, bring with them a demand for rigour and a methodology in the utilization of their contributions, thereby ensuring greater efficiency for all.

The emergence of a new market at the bottom of the pyramid makes it possible for the 4 billion people living on less than two dollars a day to benefit from a better quality of life, to regain hope and gradually enter a virtuous economic circle. It also makes us aware that certain affordable solutions imagined for and by the people at the bottom of the pyramid could create new possibilities for a different approach in developed countries.

Take for example a safe and successful cataract treatment developed in India for less than US$50. This innovation should be transferable to a certain degree to developed countries, where prices are currently 50– times higher.

There are many successful initiatives aiming to reduce, recycle and re-use products which help to significantly lower the consumption of raw materials and to make better use of natural resources.

In order to capitalize on these emerging opportunities, and to build new foundations for our world based on a more responsible social, economic and ecological approach, we must accept and rigorously apply three key principles:

1. Ensure that scientific and technological developments genuinely serve humankind and the environment, in the context of new constraints. This requires establishing a dialogue with all stakeholders. It also means: giving priority to efforts and investments focused on the most critical challenges; taking into account all cultural sensitivities and ensure a rigorous ethical analysis when choosing priorities; explaining to people the expected benefits of progress and reassure them that the risks are known and controlled (thereby avoiding the hostile public opinion we have seen in Europe and especially in France over some new technologies); implement these technological changes within a regulatory framework and with the most strict and wide-ranging controls possible.

2. Encourage the involvement of all people in the process of change, not only because everyone is directly concerned but also because anyone can make an inventive contribution. In this way, we can help eliminate poverty, exclusion and ignorance, which is our best weapon in the fight against insecurity.

3. Build and organize a more active solidarity. Be it between developed and emerging countries, through bilateral cooperation or among the different communities involved—scientific, industrial, societal. This must also be an intergenerational solidarity, involving young people as early as possible in the decisions which will affect their lives.

This is the approach and these are the principles which must guide BioVisionAlexandria.

The life sciences will play an especially important role in providing the progress we will need to meet the challenges of the 21st century.

The Promise and Practice of International Cooperation

Koji Omi

BioVisionAlexandria 2008 is, I believe, a conference of great significance and a valuable platform.

The progress of biotechnology in recent years has been astounding. Biotechnology can be applied in many areas, such as healthcare, food and agriculture, the environment, and energy. Given its impact on daily life, biotechnology should be used to address the problems and improve the quality of life of people in developing countries.

How should the benefits of biotechnology be spread throughout society? It is true that while new technologies are developed and used mainly in developed countries, little progress has been made in narrowing the gap in science and technology between developed and developing countries.

To change this situation, Japan and other developed countries should actively promote joint research and cooperate with developing countries in this area. Research capacities in developing economies should also be enhanced by research cooperation with developed countries, a recommendation that was made in a recent STS Forum.

We often hear concerns about the safety of biotechnology, particularly as regards genetic engineering. This includes the health-related safety of genetically-modified food products and the impact on the environment of using GMOs in open systems.

There is no doubt that we must pay attention to these safety issues. At the same time, agricultural applications of GMOs can make it possible to grow high yield crops in arid climates, while ensuring sufficient food supplies. Therefore, I think it is time to consider using GMOs more positively, taking the utmost care to ensure safety.

Another important contribution of science & technology is its use in managing infectious diseases. While it is necessary to make and provide medicine for patients, it is also essential to develop effective vaccines to conquer infectious diseases. AIDS is a typical infectious disease which requires such management. Vaccines for AIDS are under development now, but it appears difficult to develop such vaccines commercially.

I believe that such fields as AIDS vaccines development require the strong commitment of the public sector. In this context, the activities of the International AIDS Vaccine Initiative are a step in the right direction. IAVI is now planning to conduct a clinical trial in Africa for a new AIDS vaccine created using Japanese technology.

To sum up my basic idea on desirable cooperation between developed and developing countries in the field of science and technology, joint research in developing countries should be encouraged with the participation of researchers and scientists from developed countries. A portion of ODA should be used for this activity, to harness the human potential of developing countries in addition to the financial power of developed countries.

Japan is exploring ways of cooperating with developing countries in the field of science and technology, for improving quality of life in developing countries. As the chair of the G8 Summit, the Japanese Government has identified the development of Africa as a key issue.

In the field of biotechnology, pharmaceutical companies should be involved in developing new medicines, while the protection of their intellectual property rights must be guaranteed. In this context, the public sector should play a larger role.

We must all become Biologists

Effat Badr

Biodiversity is under serious threat. The Earth is currently experiencing the makings of a possible extinction crisis not seen since the last great mass extinction.

But just what is under threat?

Biodiversity occurs at three levels. There is genetic diversity, or the diversity of genes within a species. There is species diversity, or diversity among species. And there is ecosystem diversity, or the diversity of ecosystems and the richness of the different processes within a system to which genes and species ultimately contribute.

Each of these is under threat, and the biggest cause of this threat is habitat loss: in particular the conversion of land to grow crops, but also the use of pesticides and fertilizers, which reduces diversity through toxic effects.

So what should be done?

Nations must address some critical questions. These include: who owns biodiversity; who should benefit from it; what is the role of both the individual and society in protecting biodiversity; and what will happen to biodiversity if climate change remains unchecked. These questions are important for understanding and protecting biodiversity, as well as sharing equitably the often enormous commercial benefits from biodiversity.

The global environment is regulated by climate changes and by biosphere dynamics. By 2050, global average surface temperatures are expected to be between two–to–five per cent higher than today and atmospheric

CO_2 concentrations could be about 100-200 parts per million by volume higher. These changes will impact biodiversity. In addition, continued habitat conversion as well as continued exploitation of wild resources will also have an impact on the climate.

Step forward biotechnology. The technology currently at the cutting edge of agriculture and healthcare is also fast becoming a major tool in conservation biology. How So? One clear example is the introduction of crops that have been genetically modified so as not to need – or to need fewer -- chemical pesticides. The use of gene sequences to create unique fingerprints – or barcodes – to help identify and catalogue individual species is another.

Biodiversity is of course not the only challenge facing humanity. As humans continue to alter our world, both regional and global environmental problems continue to mount.

The growing power of biotechnology promises to show effective solutions. But with power comes the responsibility of making wise choices. There is much about biotechnology that we do not yet know – in particular, its environmental and social implications are yet to be fully understood. The responsibility to learn and to choose is not just for scientists and policymakers, it is for all of us.

Everyone must become a biologist. The world is our classroom.

Support for Science in the Developing World

Torsten N. Wiesel

When I was initially invited to BioVisionAlexandria, I expected to discuss my research work in vision, which was recognized with a Nobel Prize in 1981. I soon learned, however, that BioVisionAlexandria addresses global issues concerned with education, health, the environment and poverty; topics far outside my competence as a research scientist. The trouble with becoming a Nobel Laureate is that you are suddenly expected to be an expert on almost everything, and some fall into the trap. That seems to include me, as I will now discuss what action is needed to deal with problems related to the 20% of the global population who live in poverty, suffering from serious issues in terms of health, education and jobs. My incompetence is obvious: I come from Sweden and spent 40 years in a neurobiology laboratory in the United States trying to understand the neural basis of perception. For seven years I was President of Rockefeller University, and for the past eight years I have been Secretary General of the Human Frontier Science Program. So I am clearly not an expert on education, health, the environment or poverty.

In the past couple of decades, however, I have been active in a number of programs related to science education and training at an international level that are directly or indirectly involved with the developing world. Here I will briefly describe these programs and indicate why they could be relevant to the planning of future actions.

International programs

The New York Academy of Sciences, of which I was Chair of the Board of Governors for six years, has more than 25,000 members in 140 different countries. The name is misleading as more than half of its members are from outside the United States. It aims to create a global community of scientists for the benefit of humanity by advancing knowledge about science and related issues. Under the able leadership of John Sexton, Chair of its Board, and Ellis Rubinstein, its President, the Academy should have a positive impact on the major global challenges facing the world's poor. Programs such as Science Without Borders, e-briefings of scientific meetings and educational programs are now available worldwide on the Internet. It is worth noting that Jeffrey Sachs, another speaker at this BioVisionAlexandria conference, is a member of the Academy's Board.

The International Brain Research Organization is active in my own field of neuroscience. It is an independent organization formed after the Second World War and is a member of ICSU with more than 60,000 members worldwide. It is dedicated to neuroscience education, primarily in the developing world, and to facilitating global communication between brain scientists. Its annual income of US$2 million from the journal *Neuroscience* allows it to support regional committees in Africa, Latin America, the Far East and Eastern Europe, and these organize summer schools for young students. For more senior students they provide week-long courses and travel funds to attend international or national meetings. The Chair of each regional committee is a member of the main executive committee, providing each region with a voice in central policy planning, in addition to responsibility for planning in the local area. In my opinion it is important to give local authorities a strong voice in planning programs in all of the areas to be discussed at BioVisionAlexandria.

Since 2000 I have been Secretary General of the Human Frontier Science Program, an international organization devoted to funding basic interdisciplinary, innovative research in the life sciences and to supporting the advanced training of postdoctoral students outside their home countries. The program was initiated by the Japanese government 20 years ago and is now supported by 13 member countries, plus the European

Union. It is a bottom-up program as research grants must be initiated by a scientist in a member country who forms teams of two to four people from either member or non-member countries. Similarly, postdoctoral students can apply from all over the world, but the training must be done in a member country. On returning home, the student can apply for a three-year grant of US$100,000 a year to set up an independent laboratory. It is therefore a model program in science education and research in the developing world.

I have also been involved with the Pew Latin American Fellows Program, which was set up to help restore the excellence of biomedical science in Latin America following the depletion of scientific expertise during the dark decades of fascism after the Second World War. Rebecca Rimel, President of the Pew Charitable Trust, was instrumental in starting this two-year postdoctoral program, set up to train students in first-rate US laboratories. It is now more than 15 years old and has been a resounding success, with more than 80% of the students returning to their home countries. The program has regional committees that make the initial selection of candidates, and a central committee that, with help from regional chairs, selects the ten best candidates. Many former students are now among the leaders in biomedical sciences in Latin America.

The last program I will mention is the Israeli-Palestinian Science Organization, a non-political, not-for-profit organization created five years ago to foster and sustain cooperation between Israeli and Palestinian scientists and scholars. UNESCO played an important role in the creation of IPSO, which grew out of a meeting in Paris related to the annual Science for Peace day on 10 November 2003. UNESCO continues to support the program. Despite the political situation, in the past few years, teams of Israeli and Palestinian scientists have submitted more than 100 applications for funding to the international scientific council, of which nearly half have been approved. Unfortunately, the program has had serious difficulties in raising sufficient funds to support these research projects, typically on water management, agriculture, health and social issues. The organization's creation of North–South teams highlights an effective way of aiding the development of infrastructure and scientific skills in the

developing world, and shows how science can rise above conflict between countries to serve as an important tool for peace.

Conclusions

I strongly believe that science education and basic research provide the foundations for scientific, technological and economic development. Sustained improvements in living standards require major investment in education and research infrastructure, which provides the driving force for the development of health facilities, agriculture and economic prosperity.

From a background report for a meeting organized four years ago by the Third World Academy of Sciences, the Human Frontier Science Program Organization, the Wellcome Trust and the European Molecular Biology Organization, it became clear that there is an urgent need to encourage basic research in the life sciences in selected countries at different levels of development. This would require the creation of specific programs in science education and research that focus on the developing world, based on collaboration between North and South, as well as South and South. Elements of some of the programs discussed above can serve as models for such programs.

How can such programs be supported? In my opinion, some of the large amounts of funding now set aside to treat and support victims of diseases such as malaria, AIDS and tuberculosis should be allocated for building infrastructure in these countries. This would help people take full advantage of the resources so generously provided by different organizations and governments. Local governments also play a critical role in building infrastructure, and I hope that they would meet their responsibility in this.

1

GLOBAL CHALLENGES AND HOW TO MEET THEM

1

Getting Africa back to Health

Hassan Masum, Abdallah S. Daar, Sara Al-Bader, Ronak Shah, Peter A. Singer

Before the Bill and Melinda Gates Foundation, little funding was available for scientific discovery to address the major health needs of the world's poorest. The situation has now improved greatly, thanks to the Foundation's donations, along with investment from other foundations and governments and contributions from the private sector.

Many public-private partnerships, such as the Medicines for Malaria Venture and the Foundation for Innovative New Diagnostics, focus on product development to fill a hitherto largely empty product pipeline. The success of these partnerships is only now beginning to become apparent, perhaps most obviously in the fact that a malaria vaccine now seems within reach. More recent initiatives, such as the Grand Challenges in Global Health, and delivery initiatives, like the Advance Market Commitments for Vaccines, have further increased the flow of new products to address the diseases of the poor.

We applaud these initiatives, believe they require increased support, and deeply hope that as many affordable and effective products as possible will emerge from the drugs pipeline. However, now that we are beginning to see a global value chain of health innovation, the time is right to reflect on the balance between innovation in the Northern and Southern Hemispheres. At present, most of the discovery occurs in the North, for delivery in the South.

In this article we address a core question: 'How can we accelerate the science-based development of health products and services in Africa?' We answer this question by suggesting a concrete action plan, based on African voices: health convergence centers and venture funding to stimulate the development of science-based health products and services.

Before delving into how such an action plan might work, we want to address why that is the way forward. We see at least four good reasons for such a plan. First, because local entrepreneurs are in touch with local consumers, they know their needs and financial restrictions. Indeed, the Silicon Valley entrepreneur and inventor Bala Manian pointed out that he had to unlearn everything he had learned in Silicon Valley before he could effectively innovate health products in India. Second, in the long term, dependency breeds resentment. Unless they participate actively in discovery and development, citizens of the developing world may increasingly resent being excluded from the improvements in wealth and capability that flow from innovation. Third, local market demand is substantial and growing, and people want better or more appropriate health products and services that are not yet available locally. Local innovation can tap into this demand to create self-sustaining cycles of local development and delivery. Finally, ingenuity knows no borders, as global firms discover when they seek to identify talent in emerging economies. The world is beginning to tap into ingenuity in the emerging economies of India and China, but ideas and talent are still being wasted in Africa because various barriers keep ideas from getting to the marketplace and few value-added jobs are available locally.

Science-based health innovation in Africa will be different from the US model. US biotechnology developed with massive investment from public research funds through the National Institutes of Health; venture capitalists then cherry-picked the most commercially attractive prospects. The scorecard for the industry as a whole is not compelling, although some firms have done extremely well. Innovation in Africa would proceed along a very different path, perhaps more akin to the way Indian companies developed: focus initially on the immediate market needs to produce revenues, and then use that revenue to move up the value chain and grow by re-investing the earnings (Frew et al., 2007).

Is an innovation-based approach more effective than simply applying existing technologies better, such as by providing more medical services and drugs? This is a false dichotomy, as we must meet present needs and pursue future opportunities simultaneously. For example, decades ago vaccines evolved from being a scientific novelty to a mainstay of global public health. Similarly, why would anyone today want to use only bednets to fight malaria? We should pursue both approaches: bednets address the immediate humanitarian needs, and vaccines could, in the future, eliminate the need for bednets. This strategy should not be viewed as 'either-or', but rather as constructing the near and longer-term future simultaneously.

Several high-level reports from the United Nations, the African Union and other organizations have recognized the potential of the life-sciences industry to address Africa's health and environmental challenges, and to channel growing indigenous scientific and entrepreneurial capacity towards innovative health products and services. Other nations, including India, China and Brazil, have already experienced successes on this path. Surely the faster-developing and better-governed African regions can move towards joining them, especially if they focus on areas of strength and share best practices and resources among themselves. It is not easy to approach the depth of expertise and breadth of market opportunities of India or China, but a cooperating network in Africa would have the advantages of increasingly integrated regional markets, external support and prior models to learn from (including life-science and health successes in smaller developing nations such as Cuba).

Our research in Ghana, Tanzania and Rwanda indicates that key elements of science-based health innovation and commercialization do exist, but face a critical obstacle: the lack of linkages and skill flows between scientists, entrepreneurs, investors and other actors. In response, our proposed network of health convergence centers would stimulate R&D-based health entrepreneurship, and the venture fund would invest in opportunities in the network and elsewhere. The goal is to bring together science, business and capital into a critical mass of cross-learning players. We believe this will lead to the development of entrepreneurship, and of affordable health products and services focused on local needs. Ultimately, the macro-economic benefits of high-quality job creation will capture the value of indigenous innovation.

African health challenges and R&D

At present, no vaccines are effective against malaria, HIV or tuberculosis. The millions of deaths each year in Africa from these and other diseases are an economic and humanitarian disaster. Without HIV/AIDS, a report from the Commission for Africa suggests, the gross domestic product (GDP) of 33 African countries would have grown an extra 1.1% per year between 1992 and 2002 (Shisana and Letlape, 2004). The direct and indirect costs of malaria may total up to 3% of GDP in the malaria-endemic countries of sub-Saharan Africa, yet even this statistic understates malaria's long-term cumulative effects (Sachs and Malaney, 2002).

But such statistics also indicate the possibility of dramatic returns from effective health products, especially where low-cost products can treat high-prevalence diseases such as malaria. Effective investment in health innovation can boost a nation's long-term productivity and economic development.

Across the continent, investment in science and technology is increasing. Mohamed Hassan, the executive director of TWAS, the Academy of Sciences for the Developing World, describes recent progress in African scientific capacity: 'Rwanda has boosted expenditures on science to 1.6% of its gross domestic product (GDP), striving for 3% within the next five years. Research and development funding in South Africa is scheduled to grow to 1% of its GDP by 2009. Nigeria plans to invest $5 billion to create a national science foundation. Uganda, with a $30 million loan from the World Bank, will establish a fund for research initiatives to be selected through a nationwide merit-based competitive process. Zambia, with a $30 million loan from the African Development Bank, will offer postgraduate fellowships to train some 300 science and engineering students in its country' (Hassan, 2007a).

Hassan also ties this progress into broader advances in life-sciences capacity, as well as cooperation between countries of the South (Hassan 2007b). To give two other examples, the African Institute for Mathematical Sciences, in collaboration with the universities of Cambridge and Oxford, has been training a growing number of postgraduates since 2003. It aims to 'expose some of the brightest people in Africa to scientific culture

at the highest level and thereby help them acquire the tools to develop desperately-needed fundamental new technologies.' And NEPAD, the New Partnership for Africa's Development, has launched an initiative mapping the science landscape of Africa using science, technology and innovation indicators.

Investment in health R&D in Africa has already brought modest successes. The UK Medical Research Council's laboratory in the Gambia, created in 1948, is Britain's largest medical research investment in a developing country, with high-quality clinical and laboratory research and direct provision of healthcare (MRC, 2006). The Navrongo Health Research Center in Ghana, established as a field site in 1988, has grown into an international-standard health research facility; its research has brought about significant reductions in local child mortality. The TDR research and training program, set up by UNICEF, the United Nations Development Program, the World Bank and the World Health Organization, has been building health capacity in Africa for several decades. Finally, the African Institute of Science and Technology is a multi-campus initiative being developed to build a world-class technical institution, with support from IIT-Bombay, the World Bank Institute, the International Finance Corporation, and a diaspora network of African scientists and engineers.[1]

As these examples show, increased investment in science and innovation allows African countries to grow economically and develop the capacity to take control of their own destiny. In combination with improvements in governance and capacity, the UN Millennium Project report on Science, Technology and Innovation suggests building on the limited R&D investments to date, emphasizing the value of science-based development and of creating 'conditions that will enable developing countries to make full use of the global fund of knowledge to address development challenges' (Task Force on Science, Technology and Innovation, 2005).

Moreover, Freedom to Innovate, a recent report by the African Union High-Level Panel on Modern Biotechnology (2007) looks at pan-African innovation strategies and emphasizes the value of increasing African science and technology capacity, and of linking business and life sciences: 'Local

1. www.scidev.net/randd/subsahara/soboyejo and www.nmiscience.org/who_we_are.html

Innovation Areas [would] increase productivity and innovative capacity in individual businesses and in industry, and incubate new businesses that in their turn buttress innovation and expand the center.' Similarly, a Commission for Africa report (2005) recommends that the international community commit up to US$3 billion over 10 years to develop centers of excellence in science and technology. But how will the results of this science be commercialized?

Supporting African innovation

The shrub *Cryptolepis sanguinolenta* is indigenous to Africa. Practitioners of traditional medicine in West and Central Africa have long used an aqueous extract of the shrub to treat several diseases, including malaria. Its derivatives have been shown to have anti-malarial properties (Wright, 2007), and institutions in Ghana have been studying its toxicity and marketed a tea-bag formulation domestically (Simons et al., 2006)

But if the drug is to live up to its potential, many steps are necessary. So far, derivatives of the shrub have had only a minimal impact. Broader studies and trials are needed to determine its effectiveness and optimal dosage to build credibility and facilitate its export to larger markets. Production facilities and supply chains need to be built, and they must guarantee product quality to the end user. Regulatory and human-resource barriers need to be overcome. Sources for the raw material must be found that can provide a steady and inexpensive supply. All these steps, in combination, represent a quagmire for inexperienced research institutions or small entrepreneurs.

In Ghana, we met Kwabena Bosompem, a professor at the Noguchi Memorial Institute for Medical Research who developed a diagnostic test for schistosomiasis, a parasite infection. But as long as it remains stuck in his lab, it cannot help the children just a few miles away who are suffering from the disease. Meanwhile, venture capital is available, although it is rarely invested in life sciences. A good regulatory framework exists, and Ghana's health minister wants to commercialize health products. But these critical assets are not joined up, and no one can get the diagnostic test from Bosompem's lab to the villages where it is needed. Unblocking the barriers

that keep such research stuck in the lab will bring both economic and health gains. These barriers come in a range of areas, such as financing, clinical trials, intellectual property, licensing, manufacturing, delivery and understanding motivations and markets (Singer et al., 2007).

Similar barriers apply to inexpensive solutions that do not involve high-tech products. For example, we know of ways to innovate on pricing, and systems that can better deliver health products and services. In many such cases, enabling Africa to develop its capacity requires developing good ideas into real-world solutions, and then scaling these solutions up into a sustainable route to health and wealth.

We are conducting research in Ghana, Tanzania and Rwanda with the goal of understanding these barriers and finding potential solutions. We have conducted more than 100 in-depth interviews with a cross-section of entrepreneurs, scientists, government officials, civil servants, local representatives of international organizations, academics and health experts. Although this work is still in progress, we can share some early conclusions based on our analysis of the data so far.

In Ghana, we conducted an assessment and case study of innovation in the domestic health system, at the invitation of then health minister, Courage Quashigah. We interviewed 35 stakeholders from academia, government, civil society and private industry, and analyzed these primary interviews alongside research and analysis of secondary sources. Three key conclusions emerged:

Many important elements of an innovation system already exist. However, without more synergy and knowledge flows between companies and science and technology actors, it will be hard to commercialize new health technologies.

- Innovative biomedical and health R&D show the potential to be commercialized
- The financial incentives and resources for commercialization are currently inadequate

In Tanzania, we conducted a case study at the invitation of Peter Msolla, the Minister of Higher Education, Science and Technology. Like Ghana, Tanzania has many key players in the health innovation value chain and significant research capacity. Again, however, the knowledge

is not flowing between groups to bring about the commercialization of new health technologies, especially between research institutions and the private sector. Again, valuable research remains stuck in a laboratory.

We floated the idea of convergence with the various stakeholder groups, all of whom supported the idea and identified ways that such a mechanism could overcome missing linkages and accelerate the path of innovation. One participant highlighted this enthusiasm: 'I am excited by it. I think a lot of the gaps are not real gaps but more about getting the linkages to work. For me, that kind of convergence center would be a good place to get these ideas processed, so the visions of all the stakeholders are taken into consideration.'

In Rwanda, we conducted a case study in November 2007 at the invitation of Romain Murenzi, Minister of Education, Science, Technology and Scientific Research at the time, and our findings were similar. Our contacts showed a keen interest in a biotechnology convergence center, perhaps in the context of a potential biotechnology agency, with the convergence center adding innovation and cross-pollination by bringing health and agricultural biotechnology applications under one roof.

To further explore the viability of a platform to make these links, we organized workshops in Ghana and Tanzania, in August 2007 and December 2007, respectively. These workshops aimed to bring together the players with the knowledge and resources to collaboratively develop and implement the best solution for their country. Below, we explore the form such a platform could take, after first looking more broadly at opportunities for health commercialization in Africa.

Commercializing health research

In sub-Saharan Africa, very few places apart from South Africa have managed to move health R&D out of the lab and into a tested product. One of the exceptions is KEMRI, the Kenya Medical Research Institute, which has developed diagnostic kits for hepatitis-B and HIV, and has more in development. Overall, however, little research is being translated into real world deployment: 'Scientific and technological breakthroughs do not necessarily lead to the public's access to a new product. There is

no automatic, smooth transfer from laboratory to product, and then to delivery and uptake by the user' (Chataway et al., 2007).

Despite the challenges, many African markets offer opportunities, especially with the emergence of regional trading blocs that increase the size of easily accessible markets. In terms of purchasing power, 20 of the 53 African nations, with a combined population of over 260 million people, have a gross national income per capita greater than that of India (Mahajan, 2007). It may be heterogeneous and harder to serve than a single-country market of the same size, but this higher-income subset of nations illustrates the potential opportunities available to a network of convergence centers.

Other data suggest further opportunities

- According to BIO Ventures for Global Health (BVGH), the potential private market demand for effective malaria vaccines is more $100 million, with a public market demand several times greater still. It also suggests that significant potential markets exist for tuberculosis drugs, microbicides and tuberculosis and dengue vaccines
- The WHO estimates that improved tuberculosis diagnostics could yield roughly 100 million patient evaluations per year; this adds up to a substantial market, varying across countries by per-unit pricing
- The international donor community, including foundations such as the Bill and Melinda Gates Foundation, has committed substantial funds to purchase effective health products and services through mechanisms like the Global Fund to Fight AIDS, Tuberculosis and Malaria. These funds can boost the overall market demand for new, high-quality health products
- Annual spending on health in Africa by low-income consumers is estimated at US$18 billion (Hammond et al., 2007)

Some success stories have already shown that R&D-based health commercialization is possible in Africa. The South African company Bioclones has been producing and marketing recombinant human erythropoietin since 1998. Several new products are under development, including a class of antibodies for improved vaccine production. In Ghana, LaGray Chemical Company has launched an active pharmaceutical ingredient factory, producing branded generic and licensed drugs to treat the diseases of sub-Saharan Africa. The product line will include antiretrovirals, broad-spectrum antibacterials and topical anti-infectives. A To Z Textile Mills of Tanzania, Africa's largest manufacturer of malaria

bednets, is directly impregnating into the bednet fabric an insecticide that should last for up to five years. Several million nets are being produced annually, and a variety of innovative distribution channels are being explored to reduce the cost to the user.

These success stories can be built on and scaled up. Many precedents for such innovative health R&D exist in emerging economies such as India and China. In India, for example, Shantha Biotechnics has used an innovative process and cost efficiencies to bring down the price of hepatitis B vaccine from US$15 a dose to just 50 cents (Frew et al., 2007), making it possible for India to include the vaccine in its Expanded Program on Immunization. More than half of the children vaccinated in the world are immunized by products from the Serum Institute of India, a leading Indian pharmaceutical manufacturer. In China, SiBiono GeneTech commercialized the world's first gene-therapy product, for head and neck squamous cell carcinoma, and Shanghai United Cell Biotechnology is a pioneer in making available vaccines for oral cholera (Frew et al., 2009). Indeed, a growing number of health innovation success stories are emerging in other developing nations, notably Brazil, Jordan, Cuba, Mexico and Malaysia.

Africa can create its own unique path to success, but it must begin. As Rwanda's President Paul Kagame explained: 'We in Africa must either begin to build up our scientific and technological training capabilities or remain an impoverished appendage to the global economy...There is no reason to believe that Africa cannot achieve what others have achieved in these fields.'

Convergence centers can accelerate innovation

Many studies have suggested that support structures, both virtual and physical, are needed to stimulate innovation and peer learning, to nurture technologies that meet societal and economic needs, and to bring these technologies to market (see, for example, Ketels et al., 2006). Successful science parks have been nodes of change in China and India, for instance.

The scale of investment and local capacity surrounding these science parks and similar locations in North America, Europe and East Asia can be huge. The approach in Africa will have to be different, as investment and local capacity are thinner on the ground. We nevertheless believe that a similar approach is feasible in some African nations. One key to sustainability will be matching the monetary and time scales of investment to local capacity, and finding ways to concentrate and network that capacity so it can generate competitive outputs.

African nations are starting to invest in innovating infrastructure to achieve technological progress and boost business development. This is already happening in South Africa, where centers such as Acorn Technologies, the Cape Biotech Trust and the Innovation Hub have helped the creation of several successful companies. Meanwhile, in northern Africa, the Tunis Science and Technology Park contains 35 companies, in addition to two schools and a visitor center. The park's Nejib Abida is quoted as saying: 'When young engineers see all of this activity, they become less likely to pursue employment with the government, or to look abroad...We are trying to offer them space for creativity and innovation' (Wolf, 2007).

The convergence center that we suggest represents not a revolution, but an evolution from other models such as incubators, clusters and science parks. An incubator is a physical location providing space and facilities to grow a small company; a cluster is a broader construct involving a range of companies and commercialization services, a strong research base and formal and informal knowledge sharing.

A convergence center, on the other hand, can be seen as a hybrid of an incubator and a cluster, combining physical tenants with an extended virtual network beyond the physical space. It would provide both the breadth of services necessary to grow nascent scientific and entrepreneurial capacity into a fully realized cluster and the knowledge sharing and networks to accelerate this process. It would act as the focal point for a combination of science, business and capital to form new products and services while maximizing health and economic impact. A concrete example is the MaRS Center in Toronto, which was created with the explicit goal of realizing benefits from the wealth of life-sciences research in Canada.

The African model will have to be rather different, however, as noted above. An African convergence center should include three main components. The first is infrastructure: flexible tenant space along with reliable, high-quality support services (such as Internet, labs, communications, electricity and conference facilities). Ideally, it will be located close to a university or existing business cluster; indeed, a new breed of innovative African universities and business schools may be critical partners (Juma and Agwara, 2006).

The second component is the tenants and talent, selectively chosen by the center managers and investors with an eye to current competence and future potential. Anchor tenants can include established yet innovative manufacturers, pharmaceutical R&D firms, or university labs. A center could also include start-ups and smaller companies tackling new challenges, adapting a known business model or product to the local environment, or even doing contract research.

In addition to science innovators, these start-ups may be innovators in either process or price, similar to pioneers such as the Aravind Eye Care System in India that have used process innovation to provide quality eye care at unprecedentedly low prices (Ibrahim et al., 2006). If innovation is to have an impact for low-income consumers, it must work backwards, starting with what they can pay, and it must use the best technological and process ingenuity available to respond to those constraints (Prahalad, 2006). In the African context, the simple fact of overcoming constraints on delivery, price and localization can have as great an impact as developing a new treatment. Indeed, tenants will have many different pathways to generate health impacts. Four approaches are especially relevant:

- Develop a novel drug for a local disease from candidates identified by traditional medicine or biodiversity studies
- Make a cheaper or more effective diagnostic device that is both affordable and targeted to local diseases
- Decrease the local cost of preventive methods, such as insecticide-impregnated bednets for malaria prevention, vaccines or family planning devices
- Implement new delivery mechanisms, such as health-related micro-enterprise networks along the lines of Living Goods (Uganda), CareShop (Ghana) and CFWShops (Kenya)

A complementary set of tenants could include professionals who facilitate entrepreneurial success, including technology-transfer firms, law firms, management skills trainers, venture capitalists, banks and other funders. Social entrepreneurs and policy groups can help both to engage local people and to improve product adoption; as professionals better understand actual local needs by working with users, the businesses that develop will be more demand-driven, and products will be better matched to local constraints. Convenience tenants such as restaurants, clinics and internet cafés can make the convergence center an enjoyable place to be, and help encourage peer learning and serendipitous interactions.

The third component is the activities and services, starting with conference facilities and a critical mass of interesting people passing through. Training programs such as bio-entrepreneurship courses or competitions to develop business plans can connect young entrepreneurs with experienced mentors and capital. Face-to-face and virtual initiatives around common problems can bootstrap learning, engage a wider community to share solutions and business opportunities, and maintain a sense of community. And inter-regional networking (both within Africa and globally) can leverage the network of health convergence centers to trade ideas, experiences and technology.

Financing and developing convergence centers

How much will all this cost? The largest capital costs are for renting or building facilities, and these could be reduced if existing universities or labs could offer space at below-market rents. Other operating costs include salaries, equipment, entrepreneurship programs, expenditure on intellectual property, and regulatory costs and compliance at national, regional and global levels.

Our preliminary estimates are that the total outlay over the start-up period and the first five years of operation might be on the order of US$10 million per center, although this depends on many variables, such as potential donations of real estate or use of existing facilities. Individual countries may choose a larger or smaller physical center, and provide investment in cash or in kind (such as land, tax breaks and export support).

It is important to minimize fixed costs, so some locations might use a virtual network for an extended start-up phase and then graduate to the full physical set-up once they have grown to critical mass. In this staged approach, the initial virtual network would use low-cost rented or donated space and would rely on online venues for workshops and training, as well as networking between scientists and businesspeople, mentoring of start-ups, and planning the next stage of the convergence center itself. This scenario allows centers to scale up their costs over time in proportion to the opportunities they develop.

Indeed, the network of convergence centers itself should be scaled up sequentially, with earlier centers providing proof of concept and acting as learning labs for the later ones. If the first physical center is put in place early in the process, and other locations use virtual networks in spaces with low fixed costs, then all parties can learn from the implementation process and still make progress at all locations.

Partial models for such a network of centers already exist in Africa. The SEDA Technologies Program supports 17 regional technology business centers in South Africa, in specific sectors including health biotechnology. The African Incubator Network, which aims to develop a collaborative pan-African network of incubators and other business-development service providers, is currently active in many African nations, including Ghana, Kenya, Rwanda, South Africa and Uganda.

The value of such convergence centers will rise not just through them creating technology, but as they create connectivity with the right people, leading to other interactions: social innovation, mentorship, creative problem-solving and empirical testing of prototype solutions. The goal is to marry a technological focus with policy, systems and social innovation, building capacity for both sets of partners to facilitate sustainable and innovative implementation (Gardner et al., 2007).

What kind of financial income would a convergence center receive? Rental is a major component of income for successful incubators in Africa, and would cover a large fraction of operating costs. Other income could come from facilities and services owned and offered by the center, including rental of conference facilities and space for retail tenants, as well as consulting and mentoring services, and other services such as information technology or specialized labs. Centers could also offer training

for entrepreneurs, technology managers, executive MBAs or senior public officials, perhaps in partnership with an educational institution.

Each country will need to adapt the plan to suit its local circumstances, and make many and varied decisions:

- What local strengths could be initial foci for investment?
- With which institutions could a center collaborate or share space?
- What is the right balance between virtual and physical services?
- Who are the local champions and risk takers who will make it happen?
- Should the center include health delivery businesses and microfranchisers, as complementary and critical vehicles for investment?

In Ghana, during our August 2007 workshop, we helped local professionals consider some of these questions and begin to find answers. The conversations led to a specific focus on diagnostics and traditional medicine. Participants reacted positively to the idea of a health convergence center. They also recommended a task force to start the planning process, and representatives from the various ministries and stakeholders established one.

In Tanzania, in December 2007, we helped the Ministry of Higher Education, Science and Technology conduct a workshop with a cross-section of stakeholders: local entrepreneurs, academics, funders from private enterprise, government officials, philanthropic foundations and other local leaders. The active involvement of local business schools and science policy leaders led to a focus on generating a viable draft business plan for a Tanzanian center in advance, and refining it based on subsequent adaptation and planning by local stakeholders.

Funding support for capital and operational costs will be critical in the early stages, and may come from sources such as foundations, local governments and the African Development Bank, as its 2007 Strategy for Higher Education, Science and Technology includes several themes parallel to the idea of the convergence center.

By addressing the lack of incentives to invest in the kind of infrastructure that facilitates later-stage R&D, it would be possible to structure the convergence center as a non-profit facility that will be seen as a piece of critical infrastructure. Those who want to maximize the revenue of a bridge do not raise the tolls sky-high, but instead aim only to cover its costs while maximizing the value it adds to businesses and citizens, and

helping them recognize that value. Similarly, the convergence center is a bridge between science, business, capital and the many others who will benefit from its products and services.

A venture fund for health innovation

Remarkably, we know of almost no venture capital invested in life-sciences innovation in sub-Saharan Africa, except for one significant fund: Bioventures, based in South Africa. This makes it extraordinarily difficult to bring ideas to market.

A key issue for any proposed fund is finding good investment opportunities. Here, a venture fund and convergence center could be symbiotic. The non-profit convergence center could act as a magnet, attracting commercializable ideas from across an entire country; for venture funders, it would be an easy entryway for seeking investment opportunities.

An African health venture fund would also address an enormous market failure. If an established company in Africa has high revenues or land that can serve as collateral, it can borrow money, but the rates are high: commercial bank loans in Ghana and Tanzania often have interest rates of 20% or more. But a new company with minimal revenues, like many health technology start-ups, often cannot borrow money at all.

The venture fund could respond to this problem by pulling together a combination of investors. Profit-maximizing investors are the largest and most liquid pool of investors. Multiple bottom-line investors are willing to invest funds at a lower required rate of return on capital. Development banks and funds, such as the African Development Bank or the International Finance Corporation, could bring resources, expertise and risk mitigation for other investors. And foundations can offset costs and mitigate risks, for example through funding investment research or operations, so investors' funds can go directly to business opportunities.

By using a variety of financing sources, each with different expectations of return, a venture fund can reduce both the risk and the effective cost of capital, thereby increasing the range of financially viable business ventures the center can take on.

Investment in start-up companies might average US$1 million, spread over several stages of several hundred thousand dollars each, with the understanding that some fraction of those companies will fail at each stage (Novogratz, 2007). Smaller investments could be useful for prototyping or early-stage trials. Larger follow-up investments will be needed to scale up operations and production for those start-up companies that succeed.

Much of the portfolio of the proposed venture fund will probably consist of seed-stage investments. These will benefit from more advice and oversight, like that available from a new breed of companies such as Acumen Fund with a multiple bottom line approach to venture capital (Novogratz, 2007). Acumen Fund has invested in and helped develop innovative African health-product rollouts, such as A To Z's bednets and Voxiva's use of mobile phones and related technologies for health.

We suggest that investments could be spread across five countries that have macro-economic stability and a promising R&D base. The allocation per country might average US$5–10 million but the overall fund size could be $30–50 million, allowing it to benefit from economies of scale in management expenses and investment analysis capability. In each country, the convergence center would serve as a key point of entry for the venture fund.

If an experienced multilateral institution were to co-invest, it would improve the level of capital and expertise available to the fund. For example, the International Finance Corporation has invested in life-sciences funds in India (APIDC Biotech), China (BioVeda China) and South Africa (BioVentures). It has also invested directly in successes such as Bharat Biotech of India and Hikma of Jordan. Indeed, by April 2006 it had invested at least $127 million in a dozen life-sciences companies in emerging economies.

In a promising development, the International Finance Corporation in partnership with the Bill and Melinda Gates Foundation released a report in December 2007 on opportunities for private-sector approaches to health in sub-Saharan Africa. The press release states that there are plans to mobilize up to US$1 billion in investment and advisory services from 2008 to 2012, including an equity investment vehicle starting with US$100 million and growing to up to $300–350 million. These equity investments

are to be made in healthcare entrepreneurs and businesses, of which life sciences and innovation-based models will be a part.

Risks and long-term benefits

Why invest in African countries? Private equity funds have recently found Africa to be a land of opportunity. The three countries we have discussed—Ghana, Tanzania and Rwanda—have all been experiencing substantial economic growth. But we must consider the challenges.

One challenge is corruption. This is present to varying extents across the world. Measured by the Corruption Perceptions Index of Transparency International, Tanzania ranked in the same category as India, and Ghana was in the same category as Mexico. Corruption in Mexico and India may be a concern but it has not deterred growing numbers of foreign investors and partners. Despite serious challenges, inspirational African voices and investment success stories are becoming easier to find.

Another challenge is measuring financial potential. Do Africa's universities, labs and early-stage companies really have enough commercializable health innovations to make productive use of the proposed venture fund and convergence center? We have shown specific examples where the answer is yes, and companies in sub-Saharan Africa are already innovating in the health-product field. Given the presence of several research institutes and the lack of major venture funding outside South Africa, it is certainly true that more research is being conducted than commercialization. How big is this gap? How much innovative research can be pulled out to the market through commercialization initiatives? These questions can only be answered by starting the process. New opportunities also exist to tap synergies between health and agriculture.

A final challenge is financing. Will the convergence center break even financially, and is it the best use of scarce infrastructure and development funds? We believe that by developing a solid business plan with local partners, the center's leaders can understand the costs and minimize the risks. Another layer of independent checks will come from investors and funders in each country (for convergence centers) and for the region as a whole (for the venture fund), as they will each conduct their own due

diligence before investing. The physical center will have to weigh up the trade-offs between 'safe' tenants that can definitely pay the rent but do not push the envelope of health innovation, and more risky tenants who may fail but may also make enormous contributions in social or economic value in the long run.

Indeed, whatever challenges it faces, the center will help create a cadre of scientific entrepreneurs and bring them together to interact with business and financial players. In doing so, it will amplify local talents and create a new category of relationships among those involved in science, capital and funding. Along with the human benefits—training and empowerment, and long-term capacity development—the core real-estate asset is very likely to appreciate.

What would be the long-term macro-economic and social benefits? A successful health convergence center network and venture fund will create business revenues and high-quality jobs that would not otherwise exist, particularly through the accelerated growth of small and medium-size enterprises. Investors should see these benefits as part of the return on their investment in the center. This return is captured as each center incubates and facilitates businesses, which pass on their benefits to the surrounding society.

Investors concerned with this kind of return include governments, foundations, social investors and development banks. Any country that wants to compete in today's global economy must develop value-added businesses. Just as entrepreneurs saw no need to remain locked into telephone land lines (Sullivan, 2007), so African countries need not remain stuck in the low-wage economy trap, forever consigned to agricultural economies.

In the category of health benefits, we showed above that poor health imposes economic costs on any society. Reducing this burden therefore constitutes a real economic benefit. Consider malaria, for example: better malaria diagnostics could annually save the lives of up to 480,000 Africans, mainly children (Rafael et al., 2006). One approach to quantifying this burden economically is a recent Nigerian study that asked families how much they would be willing to pay for malaria treatment insurance. It found that, if the insurance and treatment were both effective, Nigerian

households would collectively be willing to pay approximately 1.8% of the country's GDP to access this insurance (Jimoh et al., 2007).

To the extent that a health convergence center generates positive health impacts, it will directly benefit the country as a whole, including savings to the health system, fewer working days lost, higher workforce productivity and long-term economic competitive advantage.

Conclusions

Given the potential benefits, the high demand and need, and the feasibility we have demonstrated here, we see a strategic opportunity to create a network of health convergence centers linked with a sub-Saharan health venture fund. Creating this critical infrastructure will help translate indigenous talent, capital and know-how into positive health and economic impacts in a sustainable way.

Our proposed approach includes several key actions. Develop the convergence centers through a country-by-country process, driven by a broad-based coalition of local experts and stakeholders who create their own solutions. Pilot a first center, apply lessons to subsequent centers, and scale up if it is successful. Consider locating centers within existing institutions to reduce costs and leverage existing centers of expertise, and explore potential synergies between health and other sectors such as agriculture.

On the investment side, link the convergence centers with a venture fund so the centers act as opportunity generators for the fund to invest in, and the fund supports many businesses in the centers. Finally, assess the potential 'deal flow' for this venture fund through research into existing health R&D that could be commercialized.

If this combination of centers and fund succeeds in the health and life-sciences area, it could serve as proof of concept for an even more ambitious goal: expanding the model to include water, energy, environment and other key technology domains. Imagine a network of implementation centers that channels funds and expertise to amplifying and facilitating local solutions, harnessing the tremendous entrepreneurial resources available into a self-sustaining improvement cycle that can tackle many other basic human needs.

A key issue is at stake here. Several African countries have invested in human capital and succeeded in creating democratic governance and stable macro-economies. Now will they enter the higher-value, knowledge-based sectors of the global economy? By tackling their own problems and implementing their own solutions, indigenous talent can combine with investment to create sustainable innovation capacity and positive health outcomes.

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2

How Food Crops can be Made More Nutritious

Gurdev S. Khush

Access to a healthy diet is a fundamental right. Yet a billion people, mostly in developing countries, go to bed hungry every day, and micronutrient deficiencies affect 3 billion people. Malnutrition limits human potential and the social and economic development of whole countries. Access to food depends on income, and more than 1.3 billion people live in absolute poverty, somehow surviving on an income of less than US$1 per day.

A further 2 billion people are only marginally better off (World Bank, 1997). That is why investment to create employment is just as important as investment in food production. The planet's increasing population is compounding the problem of malnutrition. It is likely to reach 8 billion by 2030, and 93% of this increase is expected to take place in the developing world, whose share of the population would increase from 78% in 1995 to 83% in 2020.

The most obvious element of malnutrition is the lack of protein, but deficiencies of minerals and vitamins also affect much of the world's population, particularly in the developing world. Organizations such as World Health Organization (WHO) and the Consultative Group on International Agricultural Research (CGIAR) have made fighting this 'hidden hunger' (micronutrient deficiencies) a high priority (World Health Organization, 1992; Bouis et al., 2000). They have targeted the micronutrients iron, zinc, iodine and vitamin A because deficiencies in these micronutrients are a major problem for the world's poor. An estimated 2 billion people have Iron deficiency, resulting in diminished

work performance, impaired body temperature regulation, impaired psychomotor development and intellectual performance, detrimental behavioural changes (such as decreased responsiveness and activity, and increased body tension and fearfulness), decreased resistance to infection, and increased susceptibility to lead poisoning (Dallman, 1990). Women and children are particularly at risk of iron deficiency because they need more iron for child-bearing and growth. An estimated 58% of pregnant women in developing countries are anaemic, and their babies are more likely to have a low birth weight. The WHO estimates that 31% of these children under five years of age are also anaemic.

At least 400 million people have vitamin A deficiency, and more than 100 million of these are young children. Each year, 3 million children die as a result of vitamin A deficiency, and 14 million children suffer from clinical eye problems and increased risk of respiratory diseases and diarrhoea (Sommer, 1990).

A billion people live in regions where iodine deficiency is rife, resulting in disorders including goitre, cretinism, reduced cognitive capacity and increased prenatal mortality (Hetzel, 1990). Zinc deficiency, which is also widespread, can lead to retarded growth, depressed immune function, anorexia, dermatitis, skeletal abnormalities, diarrhoea, alopecia and increased complications and mortality during childhood (International Life Sciences Institute, 1990). Zinc deficiency has also been linked to vitamin A underutilization.

Micronutrient deficiencies even affect a significant number of the population in developed countries. Taken together, they affect more of the world's population than protein-energy malnutrition (Chandra, 1990).

Tackling micronutrient malnutrition

Intervention programs, including supplementation, food fortification and education, have been successful in reducing malnutrition in specific situations, and will be needed in the future. For example, the dietary iodine supplementation program, which used iodized salt, has been effective in many countries. Such programs can be inexpensive and reach many of the populations most at risk (Hetzel, 1990). However, for iron, zinc and

vitamin A, supplementation programs are expensive and are unlikely to reach all of those at risk. They have often been suspended for economic, political and logistical reasons (Gibson, 1994).

Nutritionists agree that part of the solution to micronutrient deficiencies is convincing the population to make their diets more nutritious. So far, however, attempts to change people's eating behaviour have been largely unsuccessful — it is often difficult to make dietary changes using local foods if you are poor. But one project designed to increase vitamin A consumption among the poor in Northeast Thailand showed positive results. The project promoted vitamin-rich foods as something used by loving and caring mothers, focusing on a locally grown vegetable, ivy gourd (*Coccinia grandis*), which is rich in vitamin A and can easily be cultivated by most people. Most projects seeking to change diets, however, end up with participants returning to their old ways. Such approaches have worked only in limited settings, and require a lot of input, follow-up and education. When they are scaled up, they rarely work, so they tend not to be sustainable.

Given these limitations, breeding for seeds rich in trace minerals has been considered more effective for tackling micronutrient deficiencies. Crop varieties with mineral-rich seeds are not only useful for alleviating these deficiencies, but are also suitable for growing on trace-mineral-deficient soils. Results from Australia and elsewhere show that where the soil is deficient in a particular micronutrient, seeds containing more of that nutrient have better germination, better seedling vigour and more resistance to infection during the vulnerable seedling stage. These benefits can result in higher grain yields. So priorities for human and plant nutrition may often coincide (Graham & Welch, 1996).

A recent strategy for supplying micronutrients to the poor in developing countries involves making the staple foods they eat more nutritious by using conventional plant breeding and biotechnology. This strategy is cheap and sustainable, does not require a change in eating habits, and does not impose the recurring costs that accompany fortification and supplements. The greatest potential for improving nutritional status on a large scale involves breeding micronutrient-dense staple crops. Such 'biofortification' efforts are underway in several crops.

Increasing the amount and bioavailability of Iron and Zinc

A research project to develop improved rice varieties with high iron and zinc contents was initiated at the International Rice Research Institute in 1992, with the screening of germplasm to identify donors. About 7,000 entries have been analysed in cooperation with the Department of Plant Science at the University of Adelaide in Australia. A lot of variation was observed in the rice germplasm for both iron and zinc contents in the grain. Among a subset of 1,138 samples analysed, iron concentrations ranged from 6.3 to 24.4 mg per kg, with a mean value of 12.2 mg per kg. For zinc, the range was 15.3–58.4 mg per kg. A comparison of the iron and zinc contents of selected varieties with those of the widely grown varieties IR36 and IR64 is shown in Table 1. Traditional varieties Jalmagna and Zuchen contained almost twice as much iron and 50% more zinc than IR36 and IR64. Several aromatic rice varieties, such as Basmati 370 from India and Pakistan, and Azucena from the Philippines, also had consistently higher iron and zinc contents (Gregorio et al., 2000). In a study of several hundred wheat accessions, Ortiz-Monasterio and Graham (2000) found a four- or fivefold variation between the lowest and the highest iron and zinc concentrations; the highest concentrations were twice those of popular modern cultivars.

Table 1 Iron and Zinc contents of brown (unmilled) rice of selected varieties. (From Gregorio et al., 2000.)

	Fe (mg per kg)		Zn (mg per kg)	
Variety	**Mean**	**SE**	**Mean**	**SE**
Zalmagna	22.0	1.4	31.8	7.7
Zuchen	20.2	1.8	34.2	5.0
Xua Bue Nuo	18.8	0.8	24.3	0.7
Madhukar	14.4	0.5	34.7	2.8
IR64	11.8	0.5	23.2	1.4
IR36	11.8	0.9	20.9	1.4

Mean Values with Standard Errors

Rice varieties with high iron and zinc contents tend to be tall, traditional and low-yielding, and hence unsuitable for modern agriculture. Crosses between these traditional varieties and high-yielding varieties have

produced progeny with both high yield and high levels of micronutrients. For example, an improved breeding line with a short stature, IR68144-3B-2-2-3, from a cross of the high-yielding variety IR72 with the tall traditional variety Zawa Bonday from India, has a high concentration of iron in the grain of about 21 mg per kg in brown (unmilled) rice and a yield potential similar to that of modern rice varieties. A human efficacy study using milled rice of this variety was carried out during a nine-month feeding trial among young women in the Philippines (Haas et al., 2005). The results showed that the 17% higher total dietary iron consumption from this biofortified rice resulted in modest increases in serum ferritin and total body iron, and the response was greater in non-anaemic subjects. This study showed that the consumption of biofortified high-iron rice increased body iron by 20%.

It also seems possible to raise the micronutrient content of cereals by genetic modification. For example, Goto et al. (1999) transferred the soybean *ferritin* gene into the rice variety Kitaake through *Agrobacterium*-mediated transformation. The iron content of the transgenic seeds was as much as threefold greater than that of untransformed controls. Similarly, Lucca et al. (2001) introduced the *ferritin* gene from common beans into rice, and the resulting transgenic rice lines contained twice as much iron in their seeds as controls.

Another approach using genetic engineering for increasing the bioavailability of iron in rice diets is the elimination of phytate. This sugar-like molecule binds a high proportion of dietary iron, so the human body is unable to absorb it. Lucca et al. (2001) introduced a fungal gene for the enzyme phytase, which breaks down phytate, improving the bioavailability of iron in rice.

Rasmussen and Hatzack (1998) isolated mutants of barley that had low phytate contents. The level of free phosphate was higher in these mutants, suggesting the possibility of improving the nutritional value of crops through mutation breeding. Finally, studies at the International Center for Tropical Agriculture (CIAT) showed that certain varieties of common bean contained 60–80% more zinc than commercially grown varieties. Breeding efforts are underway to incorporate these higher levels of zinc into improved varieties (Beebe et al., 2000).

Increasing vitamin A content

Poor people whose diets primarily consist of cereal grains and tubers often have vitamin A deficiency, so the drive to increase vitamin A uptake is focusing on cereal and tuber crops.

Rice

Rice grains do not contain beta-carotene, the precursor to vitamin A. However, they do contain geranylgeranyl pyrophosphate, which can be converted to beta-carotene by a sequence of three enzymes in the vitamin A biosynthetic pathway. The three genes for these enzymes, two (*psy* and *lyc)* from the daffodil (*Narcissus pseudonarcissus)* and one (*crt1*) from the bacterium *Erwinia uredovora*, were introduced into the rice variety Taipei 309 through *Agrobacterium*-mediated transformation. Transformed plants contained one to three transgene copies. Ten plants containing all three introduced genes showed the normal vegetative phenotype, were fully fertile, and had a yellow endosperm, indicating carotenoid formation. Analysis of extracts from the coloured grains suggests that the goal of providing 2 μg provitamin A per g seems realistic (Ye et al., 2000). The rice variety Taipei 309 was used to introduce the beta-carotene biosynthetic pathway, as it is easy to transform. Further research has shown that only two genes, *psy* and *crt1*, are sufficient for the development of beta-carotene in rice endosperm. When *psy* from maize and *crt1* were introduced into the US rice variety Cocodrie, the beta-carotene level was 23-fold higher than that of transformed Taipei 309. However, Taipei 309 is not widely cultivated and Cocodrie is not suitable for growing in Asia.

The Golden Rice Humanitarian Board (see www.goldenrice.org) was established to develop rice that combines high levels of beta-carotene with ease of growing. It has set up a program to transfer the *psy* and *crt1* genes from transformed Cocodrie through backcrossing into varieties that are commercially grown in Asia. Projects are underway in six countries (India, Indonesia, Myanmar, Bangladesh, Philippines and China). The backcrossing program is most advanced at IRRI, where the popular Asian rice varieties IR36 and IR64 are being used as recurrent parents (Virk et al., 2006). The study has reached the stage where bioavailability and

food-safety evaluations are under way, and golden rice is expected to enter commercial production in 2011.

Cassava

Cassava is an important food staple for 50 million poor people, particularly in Africa, where vitamin A deficiency is widespread. Cassava roots exhibit wide genetic variation for beta-carotene, with orange-coloured roots have nine–ten times more beta-carotene than white roots (Table 2). CGIAR's HarvestPlus Program is working to identify orange-coloured clones that have superior agronomic traits.

Table 2 Average carotene content in cassava roots classified according to root colour.

Root Colour	Numerical Scale	Carotene (mg per 100 g)	Standard deviation
White	1	0.13	0.48
Cream	2	0.39	0.28
Yellow	3	0.58	0.28
Deep Yellow	4	0.85	0.17
Orange	5	1.26	0.11

Sweet Potato

Orange-fleshed varieties of sweet potato are rich in vitamin A, although white-fleshed varieties, which lack vitamin A, are more popular in Africa and elsewhere. The Kenya Agricultural Research Institute (KARI) in Nairobi has joined forces with the International Potato Center (CIP) in Lima, Peru, to introduce to women farmers some orange-fleshed varieties that are both rich in beta-carotene and have a high yield. The orange-fleshed sweet potatoes have proved acceptable both when eaten alone and as ingredients in processed foods, and their increased consumption has contributed to the alleviation of vitamin A deficiency (Hageniwana, 2000). In addition, HarvestPlus has run a project to popularize orange-fleshed sweet potato varieties among poor growers and consumers in east and southern Africa (HarvestPlus, 2006).

Maize

Maize is a major subsistence crop in much of sub-Saharan Africa and the Americas, where 17–30% of children under five years of age have a vitamin A deficiency. Most maize consumers in Africa prefer white maize, which lacks beta-carotene. A team of scientists from the Boyce Thompson Institute for Plant Research at Cornell University, the University of Illinois, DuPont Crop Genetics and the International Maize and Wheat Improvement Center (CIMMYT) in Mexico is working on improving the beta-carotene content of maize. The project analysed 300 genetic lines of maize selected to represent the global diversity of maize and identified varieties that came close to the target amount of 15 μg beta-carotene per g, compared with just 0.1 μg per g in standard varieties.

Wheat

Older bread-wheat varieties have strong carotenoid pigmentation. However, market demand has driven wheat breeding to produce wheat for white flour. The older types could be brought back into breeding program if desired.

Bananas

Researchers at the Queensland University of Technology in Australia have developed transgenic bananas that contain beta-carotene, vitamin E and iron by introducing the *psyB73* gene from maize and *crt1* from *Erwinia uredovora* as well as genes to increase the iron and vitamin E content. The university has applied for a licence to the Australian Government for the international release of these biofortified bananas.

Improving the amino-acid balance

A diet based on cereal grains is deficient in some of the amino acids required for normal growth and development, especially lysine. To solve the problem, researchers at CIMMYT have exploited the natural variation in maize germplasm to develop 'quality protein maize' (QPM). They incorporated the *opaque2* gene into maize varieties through conventional breeding, and found that this doubled the levels of lysine and tryptophan.

QPM maize varieties have been released in several countries in Africa and are grown on an area of almost a million hectares (Pray et al., 2007)

Millions of people in sub-Saharan Africa suffer from health problems associated with vitamin and mineral deficiency. The Africa Biofortified Sorghum (ABS) project seeks to find a long-term solution using biotechnology to create a 'super sorghum' that grows well in harsh environments but also contains high levels of essential nutrients. The project, funded by the Bill and Melinda Gates Foundation as part of its Grand Challenges in Global Health program, aims to develop more nutritious and easily digestible sorghum that contains increased levels of essential amino acids, especially lysine, along with vitamins A and E and more iron and zinc. Africa Harvest is partnering scientific teams from DuPont and the Council for Scientific and Industrial Research in South Africa to make this project a reality.

Biotechnology is also being used to increase the lysine content of rapeseed, corn and soybean. The introduction of bacterial genes for dihydrodipicolinic acid (DHPHS) and aspartokinase (AK) enzymes encoded by the *dapA* gene from *Corynebacterium* and the *lysC* gene from *Escherichia coli* led to a fivefold increase in the lysine content of canola, corn and soybean (Falco et al., 1995). Similarly, the amino-acid profile and total protein content of the potato was improved by the introduction of the *AMAI1* gene from the plant *Amaranthus hypochondriacus* (Chakraborty et al., 2000). The resulting biofortified potatoes have been evaluated in field trials and are now awaiting approval from the regulators (Ramaswamy, 2007).

Conclusions

One approach to providing the micronutrients missing from the diet of 3 billion people is to give them food supplements, but this is expensive in the long term. A second approach is to persuade people to eat a more nutritious diet, but this requires constant education and follow-up, and in many parts of the world it has not been easy for people to make the necessary dietary changes. Another approach is to make the staple foods that people eat more nutritious. This can be done by conventional breeding

or by transferring genes from other organisms into crops to increase their nutritional value. The challenge is immense and will require considerable effort over the coming years, but researchers are have made a promising start.

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3

Malaria can be Defeated

Joel G. Breman

Malaria has devastated tropical areas for centuries. The medical and social toll exacted by this mosquito-borne parasitic disease has caused huge losses economically and been a major contributor to the lagging economic growth in sub-Saharan Africa and elsewhere (Gallup and Sachs, 2001). In the mid-1950s, the World Health Organization (WHO) began a global malaria eradication program. Activities were based mainly on insecticide residual spraying (IRS) with DDT inside dwellings, where many species of female *Anopheles* mosquito reside before and after feeding on humans, and the use of chloroquine to treatment of patients with malaria (WHO, 2008a). The development of resistance to DDT in mosquitoes, and to chloroquine in the malaria parasite *Plasmodium falciparum*, contributed to the demise of the global program in 1970 (Table 1).

Over the past decade there has been renewed interest in malaria control and elimination. This is based on the observation that the effective application of new tools—mainly insecticide-treated bednets (ITNs) for those sleeping in endemic areas and artemisinin-based combination therapies (ACTs) for the treatment of patients, along with the selective use of IRS—can drive down morbidity and mortality, even in areas of intense transmission (WHO, 2008b). Malaria has even been eliminated from some recently endemic areas, including Mauritius and some Middle Eastern countries.

These successes have triggered such optimism that the Bill and Melinda Gates Foundation, the WHO and malariologists are once again talking about eradication, albeit not until 2050. The promising operational success in malaria control has resulted directly from progress in antimalarial drug

Table 1 Reasons Why Countries Failed to Eliminate Malaria during the WHO Global Malaria Eradication Program, 1955-1971.

1. Failure to keep the plan of operations current.
2. Weak monitoring of operational activities and epidemiological situations.
3. Inadequate surveillance of morbidity, mortality and incidence.
4. Inadequate training of medical staff.
5. Imprecise diagnostics.
6. Poor supervision.
7. Inadequate human resources and low quality of staff and operations.
8. Lack of DDT supplies.
9. Staff being pulled out of the program.
10. Weak health systems.
11. Research agendas being given low priority.
12. Malaria originally stable or of medium- or high-grade intermediate stability.
13. Major population movements from adjacent countries with malaria.
14. Political instability.
15. Lacking or fluctuating political and financial commitment.
16. Internal and/or external armed conflicts.
17. Donor fatigue.
18. Poor public understanding and support of the program.

development, the manufacture of ITNs, the delivery of health services, and an improved understanding of the biology, genetics, pathogenesis and immunology of malaria, and patient management. Here I will describe the current situation, new control and elimination initiatives, and the coalitions and activities that are directed against this deadly disease.

Defining the malaria burden

A total of 109 countries containing almost half the world's population are considered endemic by the World health Organization (Figure 1). The imprecision in quantifying the malaria burden results from difficulties in clinical diagnosis, particularly in endemic areas where laboratory diagnosis is lacking and other endemic diseases abound. Although parasitaemia (the presence of parasites in the blood) is ubiquitous in young children at some point during the transmission seasons, not all fever episodes are due to malaria (Koram and Molyneux, 2007).

There may be more than 1 billion malaria cases annually, with almost 70% of them resulting from the transmission of *Plasmodium falciparum*

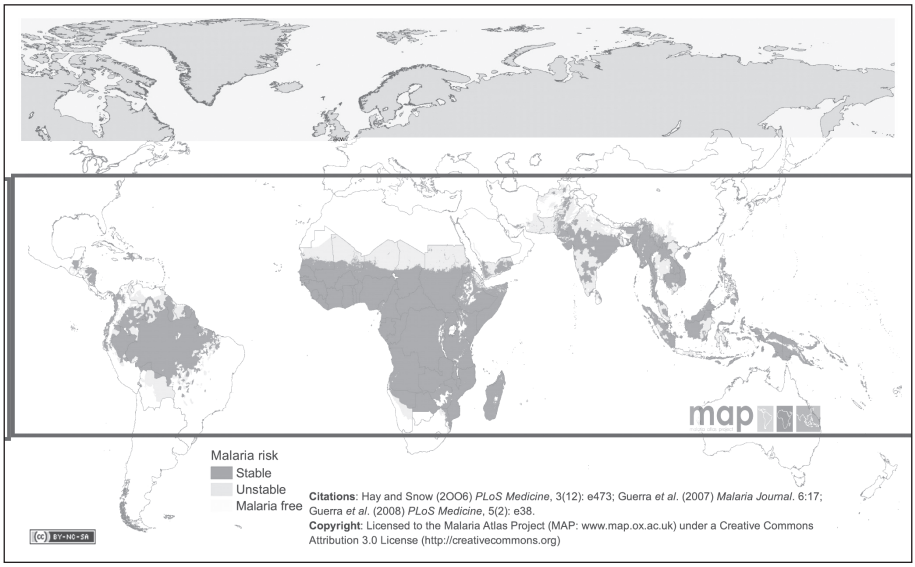

Figure 1 Malaria: Epidemiology, 2008

Table 2 Global Malaria Burden, 2005.

	Plasmodium falciparum, 2005		*Plasmodium vivax*, 2004		*P. falciparum* + *P. vivax*
Region	**Population at risk (millions)**	**Cases (millions) (range) (%)**	**Population at risk (millions)**	**Cases (millions) (%)**	**Cases (millions)**
Africa	521	365 (215–374) (57%)	50	<1	215–374
Southeast Asia	1,314	119 (66–224) (34%)	1,347	90–248 (63%)	156–472
Western Pacific	142	15 (9–26) (4%)	89	20–77 (20%)	29–103
Eastern Mediterranean	176	12 (5–25) (4%)	211	11–34 (9%)	16–59
Americas	55	4 (2–8) (1%)	78	10–28 (7%)	12–36
Europe	4	1 (0 –) (<1%)	20	1–4 (1%)	1–5
Total	2,211	515 (298–659) (100%)	2,596	132–391 (100%)	429–1,049

(Table 2). The greatest number of cases and deaths from *Plasmodium* occur in Africa (with 57%) and Southeast Asia, especially the Indian subcontinent (with 34%). Each year between 1 million and 2 million people die from malaria caused by *P. falciparum*—that's 150 to 300 every hour, day after day (Hay et al., 2004; Snow et al., 2005; Breman et al., 2007; Price et al., 2007). There are almost 400 million cases of *P. vivax* malaria each year, with more than 60% in Southeast Asia; the Eastern Mediterranean region of WHO records 12 million falciparum cases (mainly from Sudan, Afghanistan and Yemen) and up to 34 million cases of vivax malaria.

Malaria takes its greatest toll on very young children and pregnant women because of their immunological susceptibility (Figure 2) (Breman et al., 2004). Severe acute attacks of falciparum malaria can lead to anaemia, hypoglycaemia, respiratory distress, hypovolaemia and cerebral malaria; even with treatment, the fatality rate of patients with cerebral malaria is about 20%. Chronic effects can be anaemia (especially if drug treatments are ineffective), neurological and cognitive deficiencies (including epilepsy, blindness and paralysis), impaired growth and development, and malnutrition. Pregnant women with malaria are prone to anaemia and

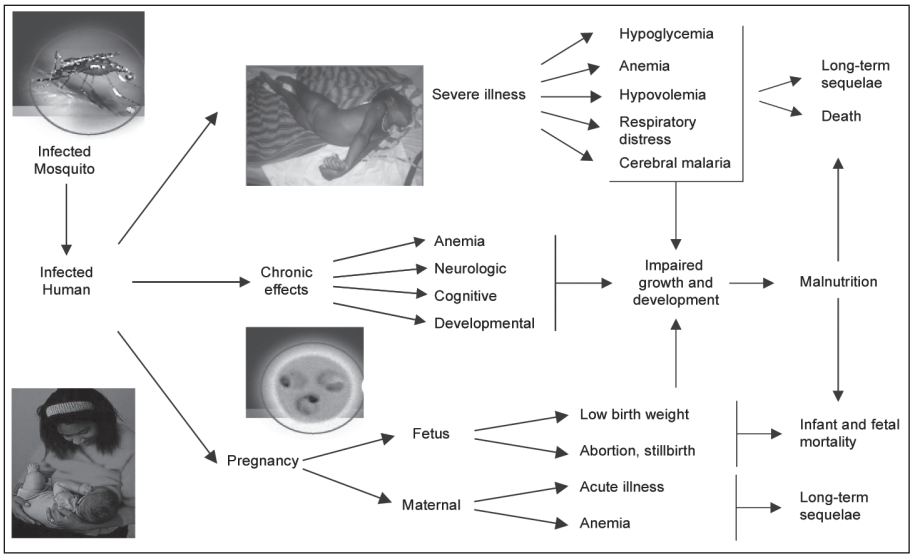

Figure 2 Manifestations of the Malaria Burden

their fetus may be aborted, stillborn or have a low birth weight (LBW) owing to parasite sequestration in the placenta; LBW is associated with high infant mortality.

Goals of malaria control programs

Africa's presidents set a number of control-related goals, strategies and targets when they met at the malaria summit in Abuja, Nigeria, in 2000. These objectives were raised in 2007 by the Roll Back Malaria Partnership (Table 3).

Table 3 Malaria Control Goals, Strategies and Targets, 2000.

Strategy	Targets for 2010 (Abuja Malaria Summit, 2000; revised 2007)
• Prompt access to effective treatment	• 80% of patients having access to and using correct and affordable treatment within 24 hours of symptom onset.
• Provision of insecticide-treated nets (ITNs)	• 80% of children <5 years and pregnant women benefiting from personal and community protection, such as ITNs.
• Prevention and control of malaria in pregnant women	• 80% of pregnant women at risk having access to intermittent preventive treatment.
• Epidemic and emergency response	• 60% of epidemics detected within two weeks of onset, and 60% of epidemics responded to within two weeks of detection.

Source: Breman and Holloway (2007).
The goal was to halve the burden of malaria by 2010 (Roll Back Malaria Partnership)

They now aim to achieve 80% of the following targets by 2010: giving people access to treatment and insecticide-treated nets; providing pregnant women with intermittent preventive treatment (IPT); and detecting 60% of epidemics within two weeks and responding to them within two weeks of notification. In addition, one of the United Nations Millennium Development Goals includes a targeted reduction of childhood mortality by 67% by 2015 (equivalent to 4.3% per year) (Wagstaff et al., 2006).

Most of the objectives of the malaria program address activities or process indicators, rather than specific malaria-related manifestations that cause disease and death. Breman and Holloway (2007) have defined several neurological, metabolic, haematological, biochemical

and parasitological conditions that require clinical and epidemiological diagnosis, quantification and management. Important malaria-associated conditions and pathologies, such as low birth weight, bacteraemia, meningitis, malnutrition and HIV infection, often require assessment in patients with malaria (Berkley et al., 2009). This requires laboratory and clinical staff to be trained and retrained, families and communities to be educated, and equipment and supplies to be provided to health units and staff, along with adequate supervision, including check sheets to assure that procedures are performed correctly.

Defining control, elimination and eradication

Control is the reduction of malaria (or other diseases) to a level that is no longer a public health problem or that is acceptable to the community. Elimination is the reduction of disease transmission in humans to zero in a defined geographic area. Eradication is the global elimination of human disease. Countries and areas that achieve elimination will face cases being imported from endemic areas, and these require prompt detection and containment to prevent the disease becoming endemic again. For countries that achieve disease elimination and eradication, a sensitive surveillance system that can detect and respond to cases if they arise is mandatory. Surveillance is the key to disease control.

Endemic countries, strategies and interventions

The WHO has divided the currently or recently endemic countries into four groups: those that have never had malaria or have eliminated the disease; those that have recently qualified for certification of elimination or that have conditions amenable to elimination (25 countries); countries with generally unstable malaria that are amenable to sustained control and can achieve elimination with current tools (32 countries); and countries with intense stable transmission and a relatively poor health infrastructure (47 countries). These 47 countries with the greatest problem are located mainly in sub-Saharan Africa and are in the 'scale up for impact' category,

needing more time to reap the benefits of research to assure that disease transmission is interrupted (Table 4) (WHO, 2008c).

Table 4 WHO Categorization of Malaria Countries.

Scale-Up for Impact	Sustained Control	Elimination
Sub-Saharean Africa Angola, Benin, Burkina Faso, Burundi, Cameroon, CAR, Chad, Comoros, Congo, Cote d'Ivoire, Djibouti, DRC, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Sierra Leone, Somalia, Sudan, Tanzania, Togo, Uganda, Zambia, Zimbabwe	Sub-Saharean Africa Botswana, Cape Verde, South Africa, Swaziland	Sub-Saharean Africa Mauritius
South East Asia Bangladesh, India, Indonesia, Myanmar	South East Asia Bhutan, Nepal, Thailand, Timor-Leste	South East Asia Korea DPR, Sri Lanka
Other regions Haiti, Papua New Guinea	Other regions Afghanistan, Belize, Bolivia, Brazil, Cambodia, China, Colombia, Costa Rica, Dominican Republic, Ecuador, French Guiana, Guatemala, Guyana, Honduras, Lao Paraguay, Peru, Philippines, Solomon Islands, Suriname, Vanuatu, Venezuela, Vietnam, Yemen	Other regions Algeria, Argentina, Armenia, Azerbaijan, Egypt, El Salvador, Georgia, Iran, Iraq, Kyrgyz Republic, Malaysia, Mexico, Morocco, Oman, Republic of Korea, Russian Federation, Saudi Arabia, Syrian Arab Republic, Tajikistan, Turkey, Turkmenistan, Uzbekistan

The Global Malaria Business Plan, Roll Back Malaria Partnership 2008

The strategies used in malaria control and elimination rely on antimalarial drugs, personal protection, vector control, environmental modification, and research (Figure 3). The strategy for using with ACTs or other drugs includes: patient management; IPT of people at high risk (currently pregnant women, who can be treated with sulfadoxine-pyrimethamine, but infants and children are also being considered for IPT); ITNs for personal protection involving the use by individuals, families and communities of long-lasting insecticide (with synthetic pyrethroids) treated bed nets (LLINs), repellants and other materials within dwellings; and classical vector-control methods, including IRS with DDT or other chemicals, the larvicide of mosquito breeding

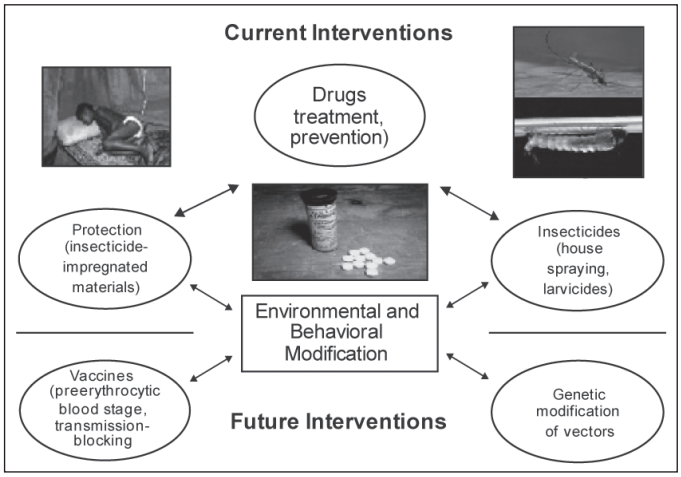

Figure 3 Control of the Malaria Burden
Breman, Allilio, Mills (2004). *Am J Trop Med Hyg. 71 (suppl2): 1-15*

sites, and the drainage and filling of areas where water collects, along with other environmental improvements to prevent mosquitoes multiplying (Sadasivaiah et al., 2007). More attention to urban malaria will be required as such centers increase in number and population in the near future. All these interventions are among the most cost-effective of all public-health tools, coming only after immunization in the cost per disability adjusted life year (DALY) averted (Table 5) (WHO, 2008c).

Table 5 Malaria Interventions are Highly Cost-Effective.

	Sub-Saharan Africa	
Category	**Cost per DALY averted ($)**	**Burden (in M of DALYs)**
Childhood immunization	1-5	Not assessed
Malaria prevention	2024	35.4
Surgical Services & emergency care	7-215	25-134.2
Childhood Illnesses	9-218	9.6-45.1
Cardiovascular disease	9-273	4.6
HIV/AIDS (prevention)	6-377	56.0
Material/neonatal care	82-402	29.8-37.7
HIV/AIDS (treatment)	673-1494	56.8
Tuberculosis (treatment)	4129-5506	8.1

DALY: Disability-Adjusted Life Year.

Control and elimination programs

The past decade has seen the setting up of the Global Fund to Fight AIDS, Tuberculosis and Malaria, the US President's Malaria Initiative (PMI), the World Bank's Booster Program for Malaria Control, and the new Malaria Elimination Group (MEG), which focuses on 'shrinking the malaria map' by working with a few countries that have unstable, low-transmission infection, good control programs and health infrastructure, political stability and political will (Breman, 2009). Since the Global Fund was established in 2002, more than 70 million nets have been distributed, 74 million drug treatments have been given and more than US$3 billion has been devoted to malaria, of which US$1.57 billion was granted to 28 countries in November 2008. Since 2005, the PMI has committed $1.25 billion to malaria activities in 15 African countries: Angola, Benin, Ethiopia, Ghana, Kenya, Liberia, Madagascar, Malawi, Mali, Mozambique, Rwanda, Senegal, Tanzania (including Zanzibar), Uganda and Zambia. The Bill & Melinda Gates Foundation contributes about US$200 million annually to malaria research and control activities, and many other US organizations have provided funding for control and research (Table 6). The WHO's

Table 6 US Funding for Malaria Activities, 2007–2008.

	2007 (million US$)		2008 (million US$)	
Foundations	214.4	(Gates 194.2)	230.9	(Gates 210.8)
Corporate	9.5	(ExxonMobil 9.0)	10.4	(ExxonMobil 10.0)
USAID bilateral	248.0	(PMI 172)	350.0	(PMI 300)
CDC	9.0		9.0	
DoD	24.6		23.1	
NIH	90.2		90.2*	
USG to GFATM	181.0		212.5	
Total	776.7		926.1	

*Provisional.

USAID, United States Agency for International Development; CDC, Centers for Disease Control and Prevention; DoD, Department of Defense; NIH, National Institutes of Health; USG, United States Government; GFATM, Global Fund to Fight AIDS, Tuberculosis and Malaria

Source: Global Health Council, 2008

Global Malaria Programme and the Roll Back Malaria Partnership provide advocacy and coordinate technical support to national programs in conjunction with WHO regional offices.

Progress in malaria control

Results

There have been substantial decreases in the number of malaria cases, deaths and hospital admissions in several countries over the past few years. Particularly impressive are the decreases in malaria resulting from the Lubombo Spatial Development Initiative in southern Africa (Swaziland, the KwaZulu-Natal Province of South Africa, and the Mpumalanga Province that borders Mozambique). The spraying of houses with DDT followed a major epidemic in southern Africa in the 1990s. IRS was complemented by the provision of ACTs for treatment and resulted in a decrease in cases from more than 60,000 in 2000 to less than 5,000 in 2005 (Sharp et al., 2007). Dramatic decreases have also been documented in Rwanda, Eritrea, Malawi, Zambia, Zanzibar, Madagascar and parts of Ethiopia. In Asia, Vietnam and Sri Lanka have achieved success with recent malaria control, as have many countries in the Americas (Breman and Holloway, 2007; WHO, 2008a).

Sustainability is crucial when dealing with such a resilient infection as malaria. A well-functioning disease surveillance system is essential so that trends can be monitored closely. Epidemics in the late 1960s and late 1980s in Sri Lanka show how malaria can resurge if control measures lapse. Similar resurgent epidemics have occurred in India and Madagascar in the 1980s and 1990s.

Research

Research is directed towards developing and improving drugs, vaccines, diagnostics, vector-control methods, modelling the spread of malaria, monitoring and evaluation, surveillance, integration strategies and health systems. The development of vaccines is one of the highest priorities in malaria research. Much recent progress has been made with a pre-erythrocytic (RTS,S/AS01A) recombinant vaccine, which has provided up

to 60% protection for six months in children; this vaccine will soon enter a phase III trial in Africa. For eradication to occur it is essential that vaccines, drugs and other tools are directed towards interrupting transmission (Breman and Plowe, 2009). The development and assessment of the safety and effectiveness of gametocytocidal drugs and transmission-blocking vaccines must receive the highest priority.

The Multilateral Initiative on Malaria has been one of the most creative research coalitions since it was established in 1997. It aims to strengthen research capacity to support malaria control in Africa (Nantulya et al., 2007).

Conclusions

Malaria has devastating effects in tropical countries, particularly in children and pregnant women. The economic toll is considerable owing to the severe medical and psychological impact of the disease, which causes impaired cognition and decreased schooling for patients and results in decreased investment in tourism and in business and development projects. The recent financing of control and elimination initiatives has brought enthusiasm and increased coverage of interventions in many countries, with early positive results. But despite these succeses, there is still disparity of access, uneven use and quality of treatments by clinicians and patients, and inadequate malaria prevention in all endemic countries. Ultimately, drugs and vaccines that block malaria transmission will lead to eradication. As these and other antimalarial tools are being developed, however, research is needed to ensure the proper delivery of current strategies and the development of new initiatives.

It is expected that up to US$6 billion per year will be needed for eradication over the next ten years before the costs begin to fall from a decreasing need for treatment and more money is directed to prevention and maintenance (WHO 2008c). Countries, international organizations and foundations must make provision to cope with the current global economic crisis if they are to ensure that malaria control and elimination milestones are met. This will require both a long-term vision and a deep commitment to the cause from partners around the world.

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4

The State's Role in Public Health

Harald Schmidt

The Nuffield Council on Bioethics is an independent body that identifies, examines and reports on ethical questions raised by advances in biological and medical research. It seeks to contribute to policymaking and stimulate debate in bioethics. To this end, it has published major reports on a range of topics, including genetic screening, healthcare research in developing countries, research involving animals, and the forensic use of DNA. In January 2006, the Council set up a working party to examine ethical issues surrounding public health, and published its conclusions and recommendations in the report *Public Health: Ethical Issues* in November 2007. Here is a summary of the key findings.

Public-Health Dilemmas

Public health has been defined as 'the science and art of preventing disease, prolonging life and promoting health through the organised efforts of society' (Acheson, 1988). But whose job is it to ensure that we lead a healthy life? Is it entirely up to us as individuals, or does the state also have a role to play? And if the state does decide to intervene, what kind of intervention would be most appropriate and effective? The Nuffield report presents an ethical framework that aims to help answer the question of when and how the state should act.

Ethical theories and Mill's Harm principle

One question that was fundamental to the Council's inquiry was the relationship between the state's authority and the individual. There is a spectrum of views on this matter, from those who give priority to the individual to those who believe that the collective interests of the population as a whole are more important.

The Libertarian perspective finds that the authority of the state is limited to ensuring that members of the population are able to enjoy the 'natural' rights of man, such as life, liberty and property rights, without interference from others. A Libertarian state does not see the promotion of the welfare of its population as its proper role.

At the other end of the spectrum is what can be called the collectivist point of view.

There are several forms, for example the Utilitarian and Social Contract approaches.

The primary aim of the Utilitarian approach is to maximise utility by focusing on achieving the greatest possible collective benefit. This means that actions or rules are generally measured by the degree to which they reduce pain and suffering, and promote overall happiness and wellbeing. In principle, they may allow the welfare or interests of some people to be sacrificed if this were to increase the overall welfare.

The Social Contract approach views the state's authority as being based on the collective will of a community (for example, as expressed in a democratic vote) to live together as an enduring nation state. This position will typically favour measures to promote the welfare of its citizens, including public goods and services of all kinds.

There are, of course, many intermediate positions between these two ends of the spectrum. Essentially they would recognise that the state should uphold certain fundamental individual rights, but also that it has a responsibility to care for the welfare of all its citizens. These welfare considerations may include ensuring that all have a fair opportunity to make a decent life for themselves, and that efforts are made to level out inequalities. Positions of this kind are generally thought of as liberal.

Most modern Western States are, according to this analysis, liberal. An important question is how far it is proper for the state to introduce

programs that interfere to different degrees in the lives of its population in order to reduce the risks to the health of all or some of them. One way to start thinking about resolving this tension is provided by the 'harm principle', established by the philosopher John Stuart Mill. This suggests that state intervention is primarily warranted where an individual's actions affect others—that coercion is legitimate where it acts to avoid harm to third parties.

Mill's harm principle was not limited to preventing harm to others. He also said: 'Those who are still in a state to require being taken care of by others, must be protected against their own actions as well as against external injury.' Mill recognized that the state can rightfully intervene to protect children and other similar vulnerable people who require protection from, for example, damaging their own health. Mill also saw the importance of educating and informing people so they can make up their own minds about how to lead their lives.

The Stewardship Model

Building on Mill's harm principle, the Council identified several further issues that are important to public health, especially the role of individual consent and health inequalities.

The concept of consent is rightly at the center of the practice of clinical medicine. Consent for public-health measures, however, is more complex. The practicalities of requiring each individual to consent to population-based interventions are extremely difficult, and may be impossible when rapid action is required. Other mechanisms need to be identified.

Particular groups of people may differ in their health status, have varying health needs and respond differently to particular health programs. The uneven burden of ill health among different groups not only raises practical issues, but also the question of whether public-health programs should seek to reduce health inequalities. The Council viewed the reduction of health inequalities as central to any public-health program.

It is clear, then, that the Council felt it was important for the liberal state to look after the important needs of people both individually and collectively. In this sense, they are stewards both to individual people,

taking account of different needs arising from factors such as age, gender, ethnic background or socio-economic status, and to the population as a whole (World Health Organization, 2000; Jochelson, 2005). In our view, the notion of stewardship gives expression to the obligation on states to seek to provide conditions that allow people to be healthy, especially in relation to reducing health inequalities.

Here is a summary of the core characteristics that public-health programs carried out by a stewardship-guided state should have. We call this the stewardship model.

Concerning goals, public-health programs should:

- Aim to reduce the risks of ill health that people might impose on each other
- Aim to reduce the causes of ill health by regulations that ensure environmental conditions that sustain good health, such as the provision of clean air and water, safe food and decent housing
- Pay special attention to the health of children and other vulnerable people
- Promote health not only by providing information and advice, but also with programs to help people overcome addictions and other unhealthy behaviours
- Aim to ensure that it is easy for people to lead a healthy life, for example by providing convenient and safe opportunities for exercise
- Ensure that people have appropriate access to medical services
- Aim to reduce unfair health inequalities.

In terms of constraints, public-health programs should:

- Not attempt to coerce adults to lead healthy lives
- Minimize interventions that are introduced without the individual consent of those affected, or without procedural justice arrangements (such as democratic decision-making procedures) that provide adequate mandate
- Seek to minimize interventions that are perceived as unduly intrusive and in conflict with important personal values

These positive goals and negative constraints are not listed in any hierarchical order. The implementation of these principles may, of course, lead to conflicting policies. However, in each particular case, it should be possible to resolve these conflicts by applying those policies or strategies that achieve the desired social goals while minimizing significant limitations on individual freedom.

Third Parties

Various third parties also have an important role in the delivery of public health. These may be medical institutions, charities, businesses, local authorities, schools and so on. Corporate agents whose activities affect public health include businesses such as food, drink, tobacco, water and pharmaceutical companies, owners of pubs and restaurants, and others whose products and services can either contribute to public-health problems or help to alleviate them.

In the same way that one would not judge the ethical acceptability of individuals' actions by merely assessing whether or not they have broken the law, it is reasonable to argue that commercial companies have responsibilities beyond merely complying with legal and regulatory requirements. Genuine corporate social responsibility clearly has a role to play in public health. But if there is a lack of corporate responsibility, or a 'market failure', it is acceptable for the state to intervene where the health of the population is significantly at risk.

The Intervention Ladder

To assist in thinking about the acceptability and justification of different policy interventions to improve public health, the Council devised what it calls the Intervention Ladder. In general, the higher the rung on the ladder at which the policymaker intervenes, the stronger the justification has to be.

- **Eliminate choice,** for example through the compulsory isolation of patients with infectious diseases
- **Restrict choice,** for example removing unhealthy ingredients from foods, or unhealthy foods from shops or restaurants
- **Guide choice through disincentives,** for example through taxes on cigarettes or by discouraging the use of cars in inner cities through charging schemes or limitations on parking spaces
- **Guide choices through incentives,** for example offering tax breaks for the purchase of bicycles that are used as a means of travelling to work
- **Guide choices through changing the default policy,** for example in a restaurant, instead of providing chips as a standard side dish with healthier

options available, menus could be changed to provide a more healthy option as standard with chips as an option available
- **Enable choice,** for example by offering participation in a National Health Service 'stop smoking' program, by building cycle lanes, or by providing free fruit in schools
- **Provide information,** for example through campaigns to encourage people to walk more or eat five portions of fruit and vegetables each day
- **Do nothing** or simply monitor the current situation

To illustrate how the factors discussed so far are borne out in practice, the Council considered a number of case studies and presented recommendations for policymakers within each. Here we focus on infectious diseases and smoking and alcohol.

Infectious Diseases

In Europe and other Western countries, death rates from infectious diseases have decreased over the past century. However, such diseases still account for more than 10% of deaths and about one in three visits to the general practitioner (GP) in the United Kingdom (Health Protection Agency, 2005).

Surveillance and Control

Information about rates of infection and the emergence of new diseases is crucial for planning public-health interventions. Collecting anonymised data is not seen as intrusive, but non-anonymised data interferes more with a person's privacy. When a serious outbreak emerges, it may be necessary for governments to introduce quite stringent policies that do infringe people's liberties to control its spread, for example by isolating those who are infected.

The Council concluded that to assess and predict trends in infectious diseases, it is acceptable for anonymised data to be collected and used without consent, as long as any invasion of privacy is reduced as far as possible. It may be ethically justified to collect non-anonymised data about individuals without consent if this means that significant harm to others will be avoided. Highly intrusive measures to control infectious diseases,

such as quarantine and isolation, would only be justified where there is a real risk of harm to others that could be significantly reduced.

Outbreaks of infectious diseases can have global implications. All cases of certain serious diseases, such as SARS and new strains of influenza, must be reported to the World Health Organization (WHO). However, different countries have different capacities for monitoring and reporting infectious disease. The Council concluded that countries with a good capacity, such as the United Kingdom, should provide more assistance to developing countries to enable effective surveillance of infectious diseases.

Furthermore, there have been complicated controversies around the access to virus isolates, which are required to develop vaccines. I cannot discuss the details here, but the full report concluded that the WHO should promote the idea of viewing virus isolates as a form of 'public good' and take a flexible approach to patenting and intellectual property protection. Furthermore, the WHO should not merely facilitate access to virus isolates for commercial companies and leave the question of vaccine availability to market forces. It should use its authority to impress on pharmaceutical companies their social responsibilities.

Vaccination

Vaccination programs protect individuals against infection and, in many cases, also bring about 'population immunity'. More directive policies, such as penalties for those who do not comply, may achieve higher levels of vaccine uptake.

The Council concluded that vaccination policies that go further than simply providing information and encouragement to take up the vaccine may be justified if they help to reduce the harm to others, or protect children and other vulnerable people. This would need to take account of the risks associated with the vaccination and the disease itself, the seriousness of the threat of disease to others, and whether a directive measure would be more effective than a voluntary one.

After weighing up the evidence and the ethical considerations, the Council concluded that there is not sufficient justification in the United

Kingdom for moving beyond the current voluntary system for routine childhood vaccinations.

Alcohol and Tobacco

Excessive drinking is associated with major health problems and also affects third parties, for example through drink-driving and violence. The number of deaths from medical conditions caused by alcohol consumption doubled between 1991 and 2005 in the United Kingdom (National Statistics, 2006). For tobacco, regular smoking of even a small number of cigarettes is harmful to the health of the smoker and the people around them. In the United Kingdom, smoking was associated with one in six of all deaths between 1998 and 2002 (Twigg et al., 2004). The banning of smoking in enclosed public places in the United Kingdom was therefore a welcome development.

Increasing the tax on alcohol and restricting the hours of sale have been shown to be effective in reducing alcohol consumption. Yet the UK Government's policies on alcohol have focused on public information campaigns and voluntary labelling schemes—measures that have been shown not to be effective. The Council concluded that measures that have been found to be effective in reducing alcohol consumption should be implemented by the UK Government, include increasing taxes on alcoholic beverages and restricting the hours of sale. Since the Council's report was published, the UK Government has imposed a 6% increase on all alcohol duty rates, and these will increase by 2% above the rate of inflation in future years (HM Treasury, 2008).

The arguments in favour of banning smoking in public spaces can also be used to support banning it in homes where children are exposed to smoke. However, this would be extremely difficult to enforce without compromising privacy. The Council concluded that there may be exceptional cases where children would be at such a high risk of harm from passive smoking, for example if they had a serious respiratory condition, that intervention in the home may be ethically acceptable, although any such case would usually need to be decided in court.

Corporate social responsibility is especially problematic in the case of the tobacco industry, as the best strategy for public health would simply be not to market the product. Nevertheless, the Council believes that the industry does have a role to play in harm reduction, particularly in an international context. It is ethically inconsistent for tobacco companies advertising and selling their products in developed countries to claim corporate social responsibility and yet apply different standards for protecting consumers in different countries, depending on local laws, yet there is clear evidence that this is common practice (Action on Smoking and Health, 2009). Acting ethically is more than simply complying with the relevant laws and regulations. Policies on selling and advertising tobacco and alcohol that afford the greatest protection to consumers should therefore be adopted worldwide, and the members of the UK Tobacco Manufacturers' Association and other companies that produce or market tobacco products should implement a voluntary code of practice that makes best practice universal in terms of consumer protection.

Conclusions

The idea of a 'nanny state' is often rejected, but the state does have a duty to look after the health of everyone, and sometimes that means guiding or restricting people's choices. On the other hand, the state must consider a number of key principles when designing public-health programs, including Mill's harm principle, caring for the vulnerable, autonomy and consent (although the last two may be less important in public health than in clinical medicine). Explicit and clear justification is required if any of these principles is to be infringed. Existing bioethical frameworks are often not well suited to address the problems of public health. The Nuffield Council on Bioethics tried to address this, and its report provides a framework for thinking about, planning or implementing public-health measures.

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5

Governing in a Climate of Change

Robert J. Berg

About 40 years ago, I visited the city of Kalemie in the Democratic Republic of Congo. Kalemie is on the shores of Lake Tanganyika and was then an important port. But when I arrived, I found that the lake had for some reason risen dramatically and flooded the city, forcing people to abandon the ground storeys of their houses and live in the upper floor. It turned out that the large river leading into the lake had reversed its course. No one could explain why, but people were speculating that the level of Lake Baikal in Russia was falling quickly and that somehow this was connected to the rise in Lake Tanganyika!

But in the face of the flooding, something else troubling had happened: Kalemie's governance had completely broken down. People of every ethnic group in town—the Lebanese, the Greeks, the Chinese, the Cubans and of course the Congolese—were practically at war with everybody else. Nightly shootouts were common. Little did I know that I had stumbled into a picture of our possible future, with the climate-change crisis tearing our societies apart if we don't change the way we govern.

Changing the United Nations

I have previously discussed the sort of changes that national governments and the United Nations should consider as they address the challenges of climate change. In essence, I have suggested that each department of

government, as well as each part of our economies and our communal life, needs to rethink its functions and programs, as climate change will be the biggest challenge to governance in history.

I now think that the United Nations has to provide a lead on this. It has been enormously important in identifying climate change as a major issue and is the venue for the most significant global climate-change negotiations. But it must overhaul its own institutions and programs, for climate change presents it with an opportunity to show national governments what it means to reshape government.

I have already noted in informal remarks to the UN General Assembly that the United Nations Population Fund (UNFPA) should redouble its work, because population growth is a powerful driver of climate challenges and there is a huge demand for family-planning services. UNESCO will need to help re-tool education systems to produce citizens and cultures that live in a new world reality. The UN Food and Agriculture Organization (FAO) and the UN's Consultative Group on International Agricultural Research (CGIAR) will need to help re-engineer agriculture to cope with new ecological circumstances. In this new era, failing to make the best of genetically modified crops could prove to be suicidal. And the World Bank, the UN Industrial Development Organization (UNIDO) and the UN Human Settlements Programme (UN-HABITAT) will need to help re-design industry, our cities, and a number of low-lying countries. All this implies a need to remodel government departments and priorities at a national and global level.

Indeed as each UN agency, national department and local government makes these changes, there will be a need to mobilize human and financial resources as if our lives depended on it, which for a sizeable fraction of the world will be true.

A Long-Term Vision

These kinds of changes to governance will call for different leadership orientations. Leaders will need to have a longer time perspective. Instead of looking for short-term gain and instant political gratification, they will need to build for the future. The kind of perspective needed is that

demonstrated by a friend in Italy who told me he was thinking of planting a stand of trees on the crest of a hill because they would look good in a few hundred years. I would like to see political leaders chosen because they wanted to help their countries survive major ecological changes 20 and 30 years away.

But leaders must do more than lead for the long term; they will also need to inspire a long-term urgency to the tasks ahead. They will have to recognize that for many countries climate change will be the largest threat to security, and that countries at peace are more likely to have a better environmental record (Economist Intelligence Unit, 2008). The key factors are long-term action, urgency and a recognition that climate change is a vital security issue.

Spelling Out the Risks

The scientific community, of course, will be deeply involved in helping to reorient societies. The International Panel on Climate Change (IPCC) has shown us that international cooperation in the scientific community can help to swing opinion everywhere. But what the IPCC and other bodies are telling us about climate change is still not leading us to act.

The scientific community must spell out the risks we face. In the 1970s there was grave concern in the United States over the health and environmental risks of polychlorinated biphenyls (PCBs). Scientists and public policy leaders agreed that if there were even a one in 10,000 risk that the Great Lakes would be polluted by PCBs, that risk would be too great. So production of PCBs was banned.

Now we have moved from the remote possibility of the dangers posed by one chemical to a firm probability of major threats to the planet as a result of our fossil-fuel-dependent economic systems. Harvard economist Marty Weitzman has looked at the fat tails of the major projections of climate change (Weitzman, 2008). He found not a 1 in 10,000 chance of catastrophe, but a roughly 1 in 20 chance of a global temperature rise of 7°C or more. Such a temperature rise would lead to rapid sea-level rise, mass extinctions, the collapse of agriculture, and disruptions of ocean currents and carbon sinks. Almost no senior national and global leaders

have contemplated a response to this kind of scenario in their emergency planning.

The UN General Assembly, for example, is trying to react to climate change by considering adding a scientific capacity to UNEP, which is rather like choosing the embroidery for the armrest of one chair on the deck of the Titanic. Meanwhile, the heads of the UN agencies have a Chief Executives Board paper that says that the UN is institutionally prepared to respond well to any aspect of climate change. Settling for either of these positions is, to say the least, unrealistic.

A Key Role for Scientists

One challenge facing the scientific community is to help governments at the national level and at the UN by providing a reality check as to whether their actions are at all commensurate with the risks now evident. Nobel laureate Paul Crutzen argues that humanity is now in the Anthropocene Epoch, where we must manage the environment forever. If this is true, the scientific community will be called upon for centuries to take a leading role in our societies and institutions.

I suggest that scientific communities in each country will need to speak with one voice on such issues. This is how the IPCC has become convincing, by representing a critical mass of scientific judgment. This puts great responsibility on national and global scientific academies and implies that they must start a dialogue with the public, as well as with political leaders, that must be constructive, serious and sustained.

The key point is that because climate change is defined as a scientific challenge, scientists will have more authority than ever before to hold the actions of society to yardsticks of adequacy and appropriateness. If we are frank, we have to admit that few scientific academies are yet up to this task.

Indeed, if governments and foundations are far-sighted, they will help to strengthen national scientific academies in a great number of countries so they can become responsible partners in forming public policies in response to climate change. There may be common themes across countries, but each ecological setting will need specific responses, calling for national

academies and academic centers to partner with national policymakers. The Open Society Institute and others are working to strengthen scientific communities, but it is not yet clear that such work is intended to help them take on the leading roles I have outlined here.

At a global level, the IPCC has successfully demonstrated how to organize scientific opinion to have an impact on thinking across the world. That global role is important and the IPCC should continue its work indefinitely.

The United Nations should also have a standing scientific advisory panel to ensure that its work reflects good science, and to ensure that it maximizes the impact of its responses to the challenges posed by climate change. The panel would review the main programs of the United Nations and suggest technologies to improve the impact of its programs. The panel should also convey to scientific communities the need for new work that would benefit the operations of the United Nations, knowing that such work would have application in many countries.

Thomas Rosswall, the Executive Secretary of the International Council for Science (ICSU), has told me there have already been attempts to give the UN a really powerful and useful advisory group on science and technology. So maybe this quest is only for the Don Quixotes of the world, but I think climate change represents a perfect opportunity to give it another try.

As we think about the need for more creative governance to respond to climate change, we need to ask ourselves who in our societies formulates the most interesting responses to climate change. Such people are rare in governments, institutions and academia.

Supporting Social Entrepreneurs

Such innovators and change-makers exist, and they are now known as social entrepreneurs. These are enormously dedicated leaders who work for the public good with as much creativity and drive as private-sector entrepreneurs use to pursue profit. The Bibliotheca Alexandrina is familiar with this, as its director, Ismail Serageldin, is a brilliant example of a social entrepreneur. Ashoka, a society that has helped define the field of innovative leadership in public service while helping to network these

leaders, has selected 2,000 social entrepreneurs for special recognition. Some of these 350 Ashoka Fellows are working on socio-economic and legal innovations to promote environmental sustainability. Over time, I am hopeful that such people will turn their enormous talents to helping to devise the changes in governance needed in a world of rapid climate change.

We need to find a way to foster more widespread innovation in governance, particularly from within the public sector and the non-profit sectors in our societies. We send whole armies of people to business school to earn MBAs so they can rack up profits, but the training of social entrepreneurs in our higher-education institutions is rare. Fostering social entrepreneurs on a much greater scale seems to be vital to climate change, and to many other issues too. We need to invest in those who are likely to help us cope creatively with the environmental crisis. Beyond fine training, we need to back innovations. For example, there should be innovation funds, such as the science and technology funds proposed by Ismail Serageldin (Serageldin, 2007), so that those with a smart idea to re-engineer governance with far more efficiency, impact and sustainability will get seed money, whether they are in the UN, civil society, or the Government of Egypt. The notion of fostering social entrepreneurship is gaining salience, as Barack Obama has indicated that he will establish a White House Office of Social Entrepreneurship.

Conclusions

We know that great changes in our governance will be required. We know that science will play new and central roles. And we know that change will require creative innovation. Maybe all this can be found in one person: the scientist who is a great public-service innovator. But more likely it will be found in dream teams in which science and public-sector innovators join forces to create change.

We know that 'business as usual' will leave us all in a desperate mess. We need to give incentives, training and recognition to those with the most promise to create the movements, laws, policies, organizations and inventions that can help us reorient our economies, societies, nations and

global institutions to cope with the perilous world unfolding around us. In this mix, the roles of science and change-makers will be more central than ever before.

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6

Best Practice in Managing Intellectual Property

Anatole Krattiger

The road from sound principles to best practice in managing intellectual property rights must include a broad, clear vision of a more equitable world, because when vision is limited, action is circumscribed. One way of realizing this vision is to expand and accelerate access to life-saving and poverty-alleviating innovations in health and agriculture, especially in developing countries. Key to this move to equity are the related concepts of intellectual property (IP) and innovation management. The nature and potential of their relationship have been discussed more fully elsewhere (Krattiger and Kowalski, 2007) and are summarized here.

First, IP is a tool to foster innovation. The concept of IP exists—and is here to stay—because of its value as a business asset and an instrument for achieving humanitarian objectives. Inventions can become property, and can therefore be owned and sold, so many individuals have been encouraged to invest in innovation, based on the profit potential from resulting technologies. But because IP protection by definition—or by design—excludes competitors and encourages higher pricing, it limits and, in some cases can altogether prevent, access by some individuals and populations. But there are many ways in which IP can be distributed and used. Intellectual property should be neither feared nor blindly embraced, but managed to maximize the benefits of innovation for the whole of society, especially the poor.

Second, IP rights are a compromise and an imperfect solution, representing the search for balance between placing ideas in the public

domain and granting ownership. Historically, we have seen that this balance encourages investment, and reinvestment, in innovation, although innovation is only rarely directed to serve the needs of the poor. Fortunately, as numerous case studies have shown, the public sector can craft effective solutions that can approach or even achieve a suitable balance. This can be accomplished by using the existing IP system, especially as it addresses situations in which companies agree to donate or otherwise share their intellectual property.

Third, genius can flourish anywhere, and the emerging global systems of innovation in health and agriculture open up new prospects for innovation everywhere. This notion has profound implications for the management of innovation, technology transfer, market competition and economic development in every country. Irrespective of whether inventions are home grown or originate abroad, authoritative IP management will play a crucial role in enabling and preserving access to the resulting technologies.

Fourth, policies to promote the creation and management of intellectual property by public-sector institutions should use technology transfer to support the larger mission of the public sector and not merely be seen as potential revenues.

Finally, intellectual property has historically benefited mostly the affluent. This is due, in part, to the fact that insufficient attention has been paid by the public sector to managing IP. This lack of focused attention must be corrected. Fortunately, there is growing interest, within both the public and private sectors, in putting IP to work for public benefit, although there is currently a lack of knowledge about how to use IP appropriately and responsibly.

What are best practices?

Best practice refers to the strategies and approaches that the public sector in particular can use to achieve its goals within an evolving IP framework. They arguably represent the best or most innovative ideas in IP management and can help the public sector better mobilize the resources to take products through the process of innovation, and collaborate with the private sector through that process. Best practices, therefore, include:

- Enacting comprehensive national laws and policies
- Formulating institutional IP policies and effective IP management strategies
- Applying creative licensing practices that ensure global access and affordability
- Building institutional IP management capabilities
- Creating functioning national IP systems that include efficient patent offices and transparent IP court systems

The key implications and best practices referred to here are intended as starting points to be adapted to specific institutional contexts and national circumstances. Some practices are evolving and will depend on the context, but most are applicable across countries and continents, and within many institutional contexts.

We look forward to feedback on all of the best practices we outline, and we encourage all parties to take greater advantage of the unprecedented opportunity to strategically manage IP to benefit those who have so far been left behind. Seizing this opportunity will lead, in turn, to a healthier and more equitable world.

Key implications and best practices

The key implications and best practices that follow are distilled from Krattiger and Kowalski (2007). They are presented in four parts and are specifically aimed at four different constituencies, who need to act in concert to make innovation work:

- Government policymakers
- Senior managers, such as university presidents and R&D managers
- Scientists
- Technology transfer officers

For scientists

Inventions, inventors and innovations

Research is one of the foundations of innovation. Research leads to discovery; discovery fosters invention; inventions nourish innovation. The work of scientists is part of a larger innovation process that spans R&D

across the public and private sectors. As the creator of inventions and Technologies, your role in technology transfer is critical. So please read on.

As a scientist, you recognize the interconnected web of science, R&D, technological advance and commercial investment. Take the time to share these insights with your institution's TTO and its senior managers.

Determining how to translate an invention into an innovation that makes a difference in people's lives (economically or socially) is one of the principal reasons TTOs exist.

The emerging global system of innovation in health and agriculture creates opportunities worldwide. This key concept, that public interest can be served through private rights, has profound implications for the management of innovation, technology transfer, market competition and economic development in every country, regardless of its economic status.

Countries engaged in reforming their R&D and technology-transfer efforts often include royalty-sharing provisions for scientists in publicly funded research institutions. This often requires assignment of ownership rights to the institution and a duty to disclose inventions. This should be seen as an incentive to turn inventions into innovations that benefit society.

Access to foreign technology is integral to development, but it is also important to focus on capturing a country's national innovation potential. Through the activities of your research program, you may be positioned to facilitate the development of indigenous innovation and traditional knowledge.

Your continued interest in your invention's development is important. This will help it reach the marketplace, and benefit those who most need it but can least afford it. As the inventor, you can significantly influence how your technology is used. For example, you might request that licences reserve your right to continue research using your inventions or reserve rights for humanitarian uses of your technology.

Collaboration with private-sector entities can significantly contribute to your institution's broader participation in innovative initiatives, particularly product development.

Networks

Collaborations create contacts. Contacts build networks. Networks provide opportunities.

Collaboration is often based on establishing personal contacts and building strong professional networks. These foster the formation of collaborative research projects and are fundamental for the effective sharing of know-how and 'show-how'. Accessing other scientists' intellectual property can be brought about through networks of committed professionals.

Keep your TTO informed about your networking activities, particularly if there is a possibility of shared research endeavours. These collaborative research projects and your network in general can be starting points for technology transfer and licensing.

IP Management

Your role can best be carried out if you have good relations with your TTO. But fulfilling your role also requires an understanding of your institution's IP policy. The policy will probably cover areas such as ownership of intellectual property, conflict of interest, the handling of confidential information, and more.

The purpose of such a policy, and more importantly the purpose of your institution's IP strategy, is not just to protect your inventions, but also to control technologies and IP assets to determine how these can be managed to spur economic growth and contribute to the greater public good. If your institution does not own anything, how can it place conditions upon its use?

As your institution implements IP policies and patenting strategies, your right to publish is not jeopardized. IP protection and licensing are just one form of knowledge transfer that, if well executed, can be in the public interest.

Philanthropic donors increasingly expect to find IP management components in grant applications and to understand how IP will be used to achieve global access and humanitarian benefits. This is one reason why a close relationship with your TTO is important, as your colleagues at TTOs may increasingly be required to prepare access strategies as part of your grant applications.

When your institution conducts or commissions an IP audit, view this as an opportunity to identify the intellectual property generated in your research program, to improve and streamline the management of third-

party intellectual property (allowing you to concentrate more on research), and to contribute to the formulation and execution of an IP strategy that benefits your program and its global impact.

It is your responsibility to disclose any potential conflict of interest. Know your institution's policy on conflicts of interest. Most conflict-of-interest issues arise when procedures are not properly followed. You are not guilty of anything if you have a potential, perceived or even real conflict of interest. It is simply a matter of managing these conflicts.

Everyone in your group or laboratory should know the obligations entered into through any agreement that affects your program.

Increasingly, contracts will include milestones. Research schedules and goals may be directly linked to specific milestones, and you need to know how such milestones might impact your program.

Published information, or research tools provided by a colleague, may be covered by IP rights. This should neither deter nor distract you from carrying out good science. An awareness of basic IP management best practices will help you to understand and identify potential IP issues. Encourage your TTO to organize occasional seminars on the basics of IP management. This will aid communication with your TTO staff and answer your questions about IP management.

Laboratory notebooks and records

Good data management and accurate record keeping through comprehensive laboratory notebooks is the foundation for building a portfolio of IP assets. Essentially, best practice in scientific record keeping should be precisely the same as best practice in record keeping for the purposes of IP management.

The confidentiality of your data may be critical in ensuring global access. Data represent a valuable form of intellectual property that can be used in licensing negotiations.

Confidentiality agreements are meant to protect sensitive information exchanged between parties and are not inconsistent with public-sector missions or research publication. Confidentiality agreements rely on a culture of trust, not a culture of secrecy.

Maintain good laboratory notebooks, as this can lead to better science and easier invention disclosures, aid patent applications and ease the

preparation of regulatory dossiers. This applies to research assistants, students, postdocs and everyone else working in the lab.

Make a strong effort to document the origin of biological and other materials you use in your research, and keep a comprehensive record.

Invention disclosures and patenting

Recognize when you actually have an invention (it is generally much, much earlier than most scientists think). Invention disclosures are the first step in protecting intellectual property. Disclose early and often. But expect only a small portion of your invention disclosures to lead to patent applications.

By filing an invention disclosure with your TTO, you are initiating a dialogue. Even if the TTO does not immediately file a patent based on your first invention disclosure, it is a process that has started, and follow-up will be much easier.

Invite your TTO liaison to visit your laboratory occasionally to discuss your work with you and your research team. Discussions with technology-transfer experts, especially patent attorneys, can help you to identify inventions.

If both patenting and public disclosure are your goals, consult with your institution's technology-transfer manager before disclosure. Your institution should have a mechanism to determine whether or not a patent should be filed without significantly delaying publication. Just be aware that premature publication can lead to a loss of IP rights.

Patents often disclose more technical and scientific information than academic publications. Read published patent applications or issued patents in your field. You can access this information free of charge on the Internet.

Your institution's technology-transfer managers will need your input if they are to make strategic decisions about where to pursue foreign patent applications. You are likely to know where different competitors are located and where products arising from your research are needed.

When you disclose an invention to your technology-transfer officers, inform them of any ideas you may have on the various fields of endeavour in which your invention could be used. This will help the TTO to plan

patent applications and design licence agreements under different field-of-use licences.

Licensing inventions and marketing technologies

The 'unique selling proposition' of your invention or technology (the features, advantages or benefits it offers) may not be the science behind the technology, but your invention's use.

Technology marketing is a process by which owners of a technology create relationships between themselves and potential users that will drive technology development and availability through commercialization or other methods.

When speaking to potential licensees or investors, it is often best to stress the potential applications of your invention, in extremely simple language, rather than the superb science behind it

Your role in field-of-use licensing is essential. You can provide your TTO with valuable information on licensable components for different applications and entities.

In agreement negotiations, your role may be to share relevant information, advice and insights. In some cases, especially with collaborative research agreements, you may be an integral member of a team that will address issues such as research plans.

Detailed aspects of negotiations, such as collaboration or licence agreements, are conducted by the relevant offices in your institution. However, participate in the internal discussions prior to licensing negotiations, as your input will be important and should be valued.

Material transfer agreements are tools for gaining greater access to tangible materials from a number of sources (scientists from the public and private sectors, both in your own country and abroad).

In most institutions, you will not be authorized to sign most agreements without review by counsel or by your TTO. Know whether or not you are authorized to sign a given agreement.

Understand the obligations that are attached to different funding sources. The impact of joint public and private financial support can be complex but will increase, particularly if your institution positions itself strongly within an innovation cluster and engages in product development.

Scientists and entrepreneurs

Not all university inventors are entrepreneurs interested in being company founders, and not all founders of spinout companies from a university are the technology's inventors. Involvement as a company founder entails a greater degree of risk and commitment to move an invention to commercialization.

Participation in a spinout can be a particularly rewarding experience, financially as well as personally, as it involves the practical application of your ideas.

Much of the success of a spinout or start-up will depend on the entrepreneurial spirit at the institution. The more entrepreneurial it is, the more likely it will be that someone wants to set up a new company.

Venture-capital investors combine a broad view of the market with solid technical expertise. They can be great allies, but will impose, for good reasons, distinct conditions on the project. Be open, patient and willing to work with them.

Freedom to operate

Collaboration among scientists and the professionals who conduct FTO analyses is essential. The scientist can explain the science and technology to help others understand the materials and methods. A scientist is the expert in the area of research and can provide important leads to other scientific groups and publications.

Teams conducting FTO analyses will also need to understand precisely what the product is, how it was developed, what materials were used, and what reports were prepared. The purpose is to ascertain that all the relevant information has been considered in the FTO analysis.

The results of an FTO analysis may allow you to make better use of technologies in the public domain and inform your choice of research tools or vector constructs. The analysis also may alert you to scientific discoveries and inventions related to your work.

Knowledge of how to access, manipulate and mine patent and publication search tools for valuable information will serve you and your program well. Become versed in Internet database search skills, and ask your TTO to organize short patent-search workshops.

Maintaining IP rights, and obligations

As a scientist, you should regularly review all the agreements that relate to your projects. This specifically includes ensuring that milestones are met, royalties are paid, and that any other obligations are taken care of.

Your institution should continuously monitor patent infringements through various surveillance protocols. A lack of patent enforcement can lead to a loss of patent rights. Your role in this is important as you are well connected in the area of your research and can indicate to the TTO which companies might be using your inventions.

If your institution conducts alternative dispute-resolution procedures, such as mediation or arbitration, you might be asked to participate, particularly if aspects of your research program are involved in the discussions.

Biodiversity, bioprospecting and traditional knowledge

When working with colleagues from foreign countries, be aware that they may be authorized to make collections of biological materials only under specified circumstances, ensuring fair and equitable terms with prior informed consent. Before proceeding with joint activities, check with your institution's TTO to make sure that all the requirements have been met.

National scientific capacity increases the negotiating strengths and benefit-sharing options in bioprospecting deals.

Scientists and anyone else accessing biodiversity must answer the following questions before collecting. Under which conditions may I enter another sovereign state's territory in my scientific capacity? Under which conditions may I collect biological material and related information? Under which conditions may I carry out or export biological material and related information from that state's territory? Under which conditions may I make further use of collected biological material and related information?

The commonly held distinction between organic and biotechnology-based agriculture inhibits pragmatic approaches to creating agricultural management systems that build on local conditions, help alleviate poverty, respect local cultures and traditions, and benefit from a successful relationship with science. Reconciling organic and biotechnology-based agriculture will greatly facilitate the development of critical innovations in health and agriculture.

Technology transfer officers

The innovation landscape and intellectual property

The emerging global systems of innovation in health and agriculture open up new prospects for innovation everywhere. This has profound implications for the management of innovation, technology transfer, market competition and economic development in every country.

Innovation is complex and integral to all six components of innovation: IP management, R&D in the public and private sectors, safe and effective regulatory systems, the ability to produce new products to high standards of quality, a national distribution system in both the public and private sectors, and international distribution systems and trade in technologies. Consider this entire innovation process when making patenting and licensing decisions.

The use of IP rights is not a panacea for the management of innovation, nor is the public domain. Both public and private goods have utility and limitations. The art of innovation management lies in using both public and private goods and to manage the interface between them.

The role of the technology transfer office

The traditional mission of TTOs—to bring university-generated IP to benefit the public—is broadening, reaching the global community. Technology transfer also enhances the reputation of academic institutions and helps them achieve their missions of education, research and community outreach, ensuring social impact.

A TTO is responsible for creating incentives to move discoveries towards product development by motivating public-sector researchers, not by a promise of revenue streams, but by the satisfaction of seeing their work applied to serve the public good.

The primary role of a TTO should not be the generation of financial returns, which can take years anyway. Be realistic when making forecasts about expected income; a positive return can take eight to ten years.

Your role in communicating the use of IP tools and the benefits of good IP management is critical. It cultivates an IP management culture throughout the organization. Such communication should be directed to senior management, your institution's board and scientists.

IP policy and strategy

An IP policy should address, at a minimum, the ownership of intellectual property, conflicts of interest, conflicts of commitment, the handling of confidential information, the principles of IP licensing approaches, the sharing of income derived from IP, and any rights the institution will retain (such as for research and for humanitarian uses).

An institutional IP strategy addresses how IP management will be used to achieve global access and humanitarian benefits of the inventions and products developed at an institution. It should include how the institution deals with incoming third-party IP, how it deals with internally generated IP, and how it will out-license its IP to third parties.

IP Management

Conduct occasionally comprehensive IP audits to determine where your IP assets are, when IP protection is needed, whether there are potential IP liability issues, whether there are licensing needs and/or opportunities, and whether there are inventions to be harvested. IP audits can be useful mechanisms that form the basis for an internal review and revision of an institution's IP strategy and policy.

Technology transfer invariably brings conflicts of interest. The challenge is to manage them in a transparent and consistent manner. Most problems arise when potential conflicts are not disclosed.

All employees (and visitors in some cases) should be required to sign an invention assignment agreement on their date of arrival.

Any TTO will have a wide range of legal matters to be addressed, and procedures for working with external patents and general counsel should be well established.

Many technology evaluation approaches exist. None is perfect. Considering that each deal is highly context specific, each TTO should be able to select the best approach and adapt it to the specific circumstances.

When devising a patenting strategy, you need to make three decisions. First, should you seek patent protection? Second, what is the best patent-marketing approach? Third, what licence fees or royalties should be levied?

Agreements and their uses

A public-sector institution can use a variety of agreements to manage and protect intellectual property, regardless of whether it is owned by the institution or by licensing partners in the private sector. The key issue is to allow flexibility so that institutions can set, or negotiate, the terms that best fit their mission and goals and the purpose of the partnership.

A template agreement should be used only as a starting point for discussions. Contracts should be tailored to fit local customs and business practices. Be sensitive to cultural and linguistic differences between parties to a contract.

Your office ought to be the official repository of all agreements dealing with incoming and outgoing biological materials.

Avoid legal jargon in agreements. Instead, use short, clear sentences that are free of vague adjectives, and write in the active voice.

Confidentiality agreements rely on a culture of trust, not a culture of secrecy. Make sure that confidentiality agreements contain the necessary exceptions appropriate for the mandate of your institution.

When negotiating collaborative research agreements, involve scientists. Their input will be critical at various stages of the process.

Modes of IP protection

Trademarks are a critical, and often overlooked, option for IP protection. They can be used as stand-alone IP protection or integrated into an overall strategy for integrated IP protection.

Public-domain technologies play an important role in publicly funded research, so defensive publishing can increase the accessibility of technologies in the public domain.

There are advantages in filing provisional patent applications, such as controlling costs and providing the time to decide whether it is worthwhile pursuing a full patent application.

For any invention, evaluate whether foreign patent rights are really required. Keep in mind possible applications in developing countries; a patent may be critical to ensure access. This will require a combination of business, marketing and legal analyses.

Licensing technology and inventions

Both non-exclusive and exclusive licences can be applicable to meeting socioeconomic goals. Exclusive licences have many options, such as exclusivity limited to a certain field of use or region, or for limited periods of time.

Reserving rights for humanitarian use may require additional work and will probably not generate licensing revenue; conversely, such provisions, if used in a strategic way, are unlikely to lead to loss of revenue.

IP managers should be cautious of imitating open licensing procedures in the field of biotechnology. It is still unclear to what extent the software models of open source can be adapted to other technological fields.

Any organization engaged in high-volume licensing will find it useful to develop its own internal template agreements that are then modified and adapted to suit each special circumstance. Checklists for different types of recurring licensing negotiations should be reviewed both before and during negotiations. For the licensing of plant varieties, certain software may be useful.

Field-of-use licensing should be adopted as the preferred method of licensing whenever possible. It allows you to gain greater control while maximizing the use and value of the technology.

In a licensing agreement, the rights (or prohibitions) to sublicense and assign a licence ought to be explicitly articulated.

Licensee agreements are contracts, so a practical understanding of contract law is fundamental to negotiating and drafting good licence agreements. TTOs can ask counsel to ensure that agreements comply with national law.

Milestones

Creative licensing strategies will help your institution gain the greatest benefits from the research it conducts. Such strategies include the balancing of exclusive and non-exclusive rights, defining the field of use, setting appropriate milestones, requiring the delivery of products to developing country markets, and exercising control over pricing.

The public sector must specify in writing exactly what it wants to accomplish with a commercial partner, detailing when and how this will be achieved by articulating milestone obligations.

Avoid 'best effort' clauses in agreements. Instead, draft comprehensive contracts with articulated milestones. This upfront investment will pay off later if a problem arises.

Developing meaningful milestones that provide the appropriate balance of incentives, rewards and penalties requires detailed preparations, a sound understanding of the processes related to developing and marketing the product, realistic forecasting of product potential, and a mission-driven mindset.

Commercialization and clusters

In a dynamic innovation cluster, authoritative IP management capacity, technology transfer and licensing are all essential. Flexibility in licensing and partnership arrangements is also important.

TTOs can be a focal point for creative networking and collaboration, generating both academic and commercial success. This role in driving the success of clusters will be absolutely essential.

As the incubator concept has evolved, the range of services offered by incubators has greatly expanded. Today, incubators provide, or provide access to a broad spectrum of office, business consulting and professional services.

Taking technologies to the market

One of your responsibilities will be to bring together individuals with different backgrounds and experiences before negotiating agreements. Ideally, a team should include business strategy, marketing, legal, scientific, regulatory, production and finance expertise.

Marketing inventions should not simply be a 'push' of technologies; rather, it should be an approach that allows the needs of buyers to 'pull' inventions.

IP Management and entrepreneurship

One of the most important factors for a successful TTO is the institution's entrepreneurial culture. This is strongly influenced by the attitude and degree of support from senior management.

Spinouts are risky, but with certain factors in place they can represent the best opportunity for developing early-stage technology.

Potential investors in a spinout will ask two major IP questions. Could previously existing IP block the technology? Could your IP dominate the market and prevent others entering?

When licensing to or creating new ventures, several key attributes are essential for attracting venture-capital investment: a strong management team, a viable technology, a strong IP position, a large potential market, and a location in an environment favourable for entrepreneurship.

New ventures in developing countries have much to gain by attracting and building on international investor networks. They have the potential to open new markets and initiate new alliances.

It is necessary to strike a balance between reliance on licensing out to existing companies and investing time and resources in creating new companies.

Risk management

The role of the technology-transfer officer, and that of attorneys who may produce legal FTO opinions, is generally to advise senior management. It is a manager's purview, based on your input, to decide how to deal with the risks identified in your FTO analysis.

The FTO analysis is an interdisciplinary endeavour best executed through FTO teams. These teams, made up of legal, business and scientific professionals, are also useful for strengthening intra-institutional dialogue and communications.

For an academic or public institution, legal FTO opinions are unlikely to be needed for the majority of technology transfer functions. They would be relevant only if the institution is engaged in downstream product development and commercialization.

Monitoring and protecting Intellectual Property

Potential patent infringements should be monitored continuously through sound surveillance protocols. Action to remedy infringements is an essential part of IP asset management. The lack of patent enforcement can lead to a loss of patent rights.

Early communication with potential infringers and diligence are the foundations for policing and maintaining IP, irrespective of whether the IP is owned by a public or a private entity.

Essential to contract management is a well-organized electronic filing system. A TTO should establish such a system as early as possible and before the number of agreements and licences become excessive. An agreement management system is available at www.ipHandbook.org.

Most IP disputes should not end up in litigation, as there are many options and strategies for resolving disputes. Good contracts and good licensing practices anticipate that disputes will arise with partnerships and licences.

Mediation and arbitration can be effective procedures for settling disputes, provided they have been agreed and established in contract clauses at a time when a licence or partnership is being negotiated — and before any problems arise.

A TTO must have systematic procedures to administer, monitor and enforce its technology licences. This includes compliance with royalty payments and reporting obligations in a non-confrontational manner.

IP Training and capacity building

When scientists learn the basics of IP management, communications with the TTO will improve. Public-sector institutions should offer training to every scientist, student researcher and technician before they work in the institute's research programs.

Part of the aim of IP management training is team building, which encourages communication between your office and the scientists in your institution. It is part of creating a culture of IP awareness. It is good practice to include senior management as participants in the training sessions, especially if the training program includes case studies.

Intellectual Property, bioprospecting and traditional Knowledge

The TTO should work with senior management to establish policies and systems for accessing indigenous or traditional knowledge, bioprospecting activities and benefit sharing in an equitable manner.

Conclusions

The guidelines above provide an outlining of best practice when managing IP. If organizations follow them, they should avoid the usual pitfalls of IP management and help to create a more equitable world. For more details, see Krattiger and Kowalski (2007).

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7

Taking Responsibility for a Better Future

Richard R. Ernst

Science has endowed us with many wonderful gifts, but it also presents us with a moral dilemma. We can use our great scientific and technological prowess for either constructive or destructive purposes. The major issues arising from our science do not relate directly to the technologies themselves, but to their conscientious, responsible and fair use.

Central to making the best possible use of science and technology is education to develop societal responsibility. Only when we learn to respect the needs of others, including future generations, instead of maximizing our own personal profit, will we contribute to the world's stability, sustainability and future hospitality. But all too often, freedom and the free market are misused for selfish goals. Education may not be enough to create societal responsibility. We also need national and international laws, as well as institutions that enforce fairness and sustainability. This may sound simple, but it must be achieved in a society where profits nearly always come first.

A global problem

One of the goals of science should be to help solve the world's problems. But this is an immense challenge and will require more than advances in science and technology alone can deliver. It also needs a new spirit.

Today, competition is more important than cooperation, with respect to politics, the economy, even science. The goal seems to beat your rivals—only weaklings collaborate. To succeed, we must be first, so we run faster every day. Scientists, for example, must produce increasing results from our research in less time, so industry can throw more consumer products onto the market. Why? So the rich can consume more energy while the poor remain hungry. Where is the justice? We may be running faster, being more creative and producing more than ever before, but are we running in the right direction?

At the moment we have almost unlimited faith in technology. But this is coupled with almost unlimited faith in the free market economy and the desire for unlimited personal freedom. Together, these factors have led to the gap between rich and poor getting wider, not narrower. Society seems to have lost its ethical foundation. Cultural and ethical values, such as responsibility, compassion and far-sightedness, have been replaced by greed, exploitation, lust for power, racism and violence. This is the moral swamp where our children must live.

Our technological world has become enormously rich, but we face a moral crisis. We need novel, far-sighted and fair approaches, but where will we find them? In our politics, our economy, or the academic community? There are few governments I would fully trust, and the economy is driven by the need for financial success, leading to short-sightedness. But the academic community is relatively free from such pressures. We still have the ability to think and act freely to create a better future. We need to work with governments and the economy, but science must play a major role, standing up for honesty, foresight and responsibility. After all, we have the power to educate the next generation of politicians and chief executives.

An academic solution

Academic institutions have a key role in creating a better world, but scientists must lead by example. As Mahatma Gandhi put it: 'We must be the change we want to see in the world.' Preaching alone is not enough.

There are three things that universities can do to help create the kind of societal change that is needed:

- Develop a new spirit within universities
- Observe critically the societal disaster across the world
- Actively develop models for the global society.

Developing a new spirit

The new spirit in our universities should have four goals:

- Developing societal responsibility
- Identifying the real needs of our society
- Solving the most urgent problems with a multidisciplinary approach
- Educating society's leaders to implementing these societal goals.

First and foremost, universities are educational institutions, and this role should not be underestimated. Educating our children is the best investment in the future. To quote the seventh-century Muslim theologian Hasan al-Basri: 'Seeking knowledge at a young age is like engraving on a stone.' Much of this responsibility is in the hands of mothers and families, because education begins at home, where the children can learn the importance of partnership, and mutual respect.

Teaching in lecture halls should be reduced, as learning by doing and by trial and error is much more efficient. In this sense, education and research should not be separated, as carrying out research is the best way of learning. A motivated student learns by himself in the research laboratory, the library or in the world of work. Albert Einstein described the Swiss Patent Office where he worked as 'the worldly monastery where I hatched my most beautiful thoughts'. Looking back at his schooling at ETH Zürich, he recalls: 'It appears to me like a miracle that the modern teaching methods have not yet entirely strangled the sacred research spirit; because especially this delicate plant requires at first liberty without which it will inevitably fade.'

Today, we are in great need of responsible leaders who have skills, knowledge, comprehension and ethics. We all should learn again to dream, to have visions, and to try to implement them. We have the freedom to express our opinion on a range of subjects, and developing our own opinions is far more valuable than merely striving to avoid making errors. It was the former German President Roman Herzog who said: 'Without critical opposition, without the engagement of relentless thinkers, a

society will degenerate. We need embarrassment and disagreement; we need impertinence and questions of independent brains.' Academics should operate on two levels: on the basic research level, to acquire depth and knowledge, and on a societal and global level, to gain breadth and to comprehend the world as a whole.

We should also break down the barriers between natural sciences, humanities and social sciences at our universities. Perhaps this will reveal the path to more comprehensive wisdom. There is much complementarity between science and art, between rationality and emotionality, between wisdom and compassion, and between materialism and spirituality. I like the metaphor of a two-legged person who has both a professional leg and a passionate leg; it is so much more efficient to walk on two legs. We should build bridges across the divide between rich and poor, between developed and developing countries, and between religions.

We cannot create a fairer world without ethics. One source of ethics may be philosophy. For example, in his treatise The Principle Responsibility, Hans Jonas states that 'the application of science results demands ethics'. We can also gain our ethics from religion: from Islam, Christianity or Buddhism. In our search for values, we find, perhaps surprisingly, that all the major world religions have the same ethics; only the languages are different. Perhaps this fact will make it much easier for different religions to coexist.

In his remarkable book Excellence Without Soul, the former dean of Harvard College, Harry R. Lewis, claims: 'The great universities, the universities that educate a disproportionate share of the nation's future industrial, political, and judicial leaders, have a very hard time explaining the overall point of the education they offer. Anything resembling moral principles or suggestions of greater values has been isolated within the curriculum if not removed from it entirely.' He also writes: 'The students are smarter, the faculty more distinguished, even the pedagogy is better—but students are less challenged than ever to grow in wisdom and to become the responsible leaders on whom the fate of the nation will depend. The professors have become more and more narrow in expertise in order to secure tenure. In recent years the university has had its head turned ever more by consumerism and by public relations imperatives, to the detriment of its educational priorities for its students. In short, money

and prestige rule over principle and reason. Harvard is a case study of how the greatest universities have lost their educational souls at the same time as they have achieved dazzling excellence.'

To prevent this kind of development, we have to appoint teachers with vision and societal and global responsibility, who emphasize the global context in their lectures and who stimulate interdisciplinary discussion groups on societal questions. As the nineteenth-century Afghan warlord Nawab Jan Fishan Khan pointed out, 'the candle is not there to illuminate itself'.

Observing societal disaster

Let us climb onto the ladder, to observe and try to understand our world, and develop models of a better future. In this context, we must mention three key areas: politics, the economy and ecology.

Perhaps the most important of these is politics, where justification counts more than justice. It seems that the world has lost its equilibrium of power, as most of the military might is concentrated in the United States, with the rest being relatively powerless. The US journalist Robert Kagan described this situation in this way: 'The US cooks the dinner. The EU does the dishes.' This is a convincing view and not very far from the truth. The United States is extremely powerful and can defend its national interests without restrictions. Just remember its resistance to the Kyoto Protocol on climate change, the vote against the Human Rights Council, the blocking of the anti-landmine convention, the rejection of the Convention on the Rights of the Child, and its rejection of the International Criminal Court.

Given this centralization of power, Europe, Asia and Africa can contribute little on their own. The strengthening of international organizations is therefore essential for global stability. The present form of the United Nations and the World Trade Organization should be reconsidered, and the International Criminal Court and the World Future Council should be strengthened. Joseph E. Stiglitz, who won the Nobel Prize for Economics in 2001, said: 'We can not go back on globalization; it is here to stay. The issue is how we can make it work. And if it is to work, there have to be global institutions to help set the rules.' But this is not a new problem; back in 1932, Albert Einstein wrote to Sigmund Freud: 'The

quest for international security requires that each nation unconditionally surrenders some fraction of its liberty of action, of its sovereignty.'

What has Europe achieved so far? I view European unification as a glimpse of hope in a dark world. However, it is disappointing that it excludes the black sheep in the heart of Europe: Switzerland. The European Union could serve as a role model for East Asia, South Asia or especially the Middle East.

Second, we must consider economy, represented by a well-dressed monkey, standing in for the Economic Human, Homo economicus. As Adam Smith wrote in The Wealth of Nations in 1776: 'It is not from the benevolence of the butcher, the brewer, or the baker that we expect our dinner, but from their regard to their own interests.' In fact, Adam Smith was a man of high morals and he had faith in the positive side of humans. But his quotes, taken out of context, can explain many current attitudes. They may provide a clue to increasing wealth for some, but they point the way to a decay of values. The upward-pointing curve of the ratio of the salaries of chief executives to those of average workers illustrates the point. This curve does nothing to help preserve values such as culture, ethics, compassion, respect, tolerance, understanding, responsibility and sustainability. It is well known that money-mindedness corrupts. Why not give our chief executives bonus certificates that they can spend exclusively on charitable purposes?

In the context of globalization, we should remember that the global market is not a lemon to be squeezed for profits, but an obligation for global responsibility.

Following Adam Smith, egoism is the driving force for all our actions. An individual's own profit provides the incentive that drives our activities. Responsibility would be a more sustainable driving force. Instead of seeking personal gain, we should ask ourselves: what does society need of me? In this sense, the term 'free market economy' should be replaced by the term 'responsible market economy'. Kofi Annan, former secretary-general of the United Nations, outlined such an approach in the Global Compact. He listed ten principles that, if followed, would lead to a significantly better economic system.

Finally, we must consider ecology. Think of the charming picture where a man comes out of his house to tell the children playing in the backyard: 'You need to go inside to get some fresh air.' And you may know the image in Science magazine showing George W. Bush disappearing in his self-produced smoke. The United States is certainly destroying our environment. It doesn't help that the worst effects of pollution and climate change occur in counties remote from the source of the problem.

Climate change is expected to have catastrophic effects for many countries, particularly those in the developing world. But some countries will fare less badly, or even benefit from global warming. Climate change may therefore widen the gap between the haves and the have-nots. Unfortunately, it seems that Indian writer Arundhati Roy was right when she wrote: 'The American way of life is simply not sustainable. Because it doesn't acknowledge that there is a world beyond America.' Unfortunately, this American disease has infected many other countries too. The first law of sustainability is this: minimize your dependency on unnecessary commodities, and disregard the irresponsible sales promotion by greedy industries that want you to remain hungry for senseless consumption.

Developing models for global society

If we are to develop societal responsibility, academic teachers should be more active outside our institutions. It is up to academics to conceive new approaches for solving the societal and environmental problems we will face in the future, as well as providing knowledge, inventions and education. Only when we provide long-term solutions to these problems will we deserve society's support in terms of finances and autonomy.

At ETH Zürich there is the Collegium Helveticum, a think-tank for conceiving ideas that might stimulate beneficial development. It does not seek growth in monetary terms, but in global responsibility and sustainability. Many promising ideas have already been formulated, such as the concept of a Global Marshall Plan by Franz Josef Radermacher. But more creative ideas are needed.

I view the function of academia as having a role in driving a vehicle. The passengers are the members of society, who must be kept in a good mood by the smooth-tongued politicians to stop them jumping from the vehicle. Industry provides the power that pushes the vehicle forwards at

maximum speed, irrespective of the direction, even if it is heading for hell. The only things that count are speed and profits. Let us hope that the steering wheel is in the reliable hands of the academic community, who feel responsible for steering a beneficial course.

Practical steps

Let me mention a few recent activities at ETH Zürich. Three years ago, ETH Zürich celebrated its 150th anniversary. To mark the occasion, 150 of its professors took to the streets of Zürich for public teaching. Small pavilions were set up in the city, and over a period of three weeks there were 430 lectures, with barely an empty seat. We provided information and started a dialogue, hoping for public feedback. It proved to be a surprising success.

At the same time, we installed a hands-on Experience Park near Zürich's central railway station. This attracted 220,000 visitors who performed their own experiments in a demonstration of lifelong learning.

Last year we had a 'European Researcher's Night', with two remote science display areas being established by the lake. On boats going back and forth between the two areas, researchers talked about their own personal research experiences. This also turned out to be a great success.

These kinds of promotional science activities have to be started at an early age. The Children's University in Zürich, which teaches children science, is an important model in this context. Vacation courses for children in a chemistry lab can be equally fascinating and provide truly unforgettable experiences.

All these activities lay the foundations for a better future based on knowledge and on considerate behaviour. The most important function of universities is to educate responsible and innovative leaders with long-term vision who are willing to serve society. They will become society's pathfinders.

We should not forget the wisdom expressed by François Rabelais: 'Science without conscience is the death of the soul.' Finally, this quote from Karl Popper sums up why we should remain active and share responsibility for a beneficial future: 'Optimism is our duty. We are all jointly responsible for what will come.'

2

THE PROMISE AND PRACTICE OF INTERNATIONAL COOPERATION

8

Reflections on Scientific Cooperation Between Germany and Egypt

Christian Hülshörster and Mahmoud Bahgat

Scientists in Egypt often speak of the golden age of Muslim scientific achievement about 1,000 years ago, during the time of the Abbasid caliphate in Baghdad and the Umayyad rule in Spain. The Muslim scientist al-Khwarizmi became known as the 'father of algebra', and the 'house of wisdom', founded by the Abbasid caliph al-Mamun between 813 and 823, brought together some of the greatest minds of all time. In Cairo, in 1005, the Fatimid caliph al-Hakim opened the *Dar al-hikma*, modelled on al-Mamun's *Bait al-hikma* in Baghdad. For many people in the West, this is 'lost history', as Michael Morgan called it in a recent book on the 'enduring legacy of Muslim scientists, thinkers and artists'. For many Muslims, however, it is a source of collective pride.

But the Muslim world has been unable to keep this tradition of scientific achievement alive. Egypt has the highest number of researchers in the Arab world and the most R&D units, but the output is disappointing. From 1995 to 1999, Egyptian researchers registered just 22 patents with the US Patent and Trademark Office, compared with 9,984 from South Korea. Public investment in R&D is extremely low, around 0.1% of GDP, and Ahmed Zewail, one of four Egyptians to win a Nobel Prize, spent almost his complete career at the California Institute of Technology in the United States.

The *Arab Human Development Report*, first published in 2002, has brought this failure of the Muslim world once more to everybody's attention. The reasons behind it are manifold, and this is not the place to discuss them in detail, but everybody dealing with scientific and academic cooperation in the Muslim world is well advised to keep this 'lost history' in mind.

To a certain extent, it explains the interest in the media about this topic.

The current status of R&D in Egypt may be disappointing but the country, and indeed the whole region, has plenty to offer: 'The region's competitive advantage lies primarily in the availability of high-quality human resources,' stated the *Arab Human Development Report* (2002). Considering Egypt's serious deficiencies in higher education, it still produces each year an impressive number of university graduates with great potential.

The history of German–Egyptian cooperation

There has been scientific cooperation between Germany and Egypt for at least 150 years. In 1850, the physician and parasitologist Theodor Bilharz came from Tübingen to Cairo and gained scientific recognition through his discovery of *Schistosoma haematobium*, a trematode worm that causes the disease bilharzia. In archaeology, the German Archaeological Institute celebrated 100 years in Egypt in 2007. The German Academic Exchange Service (DAAD) can look back on almost 50 years in Egypt, and its office in Cairo continued to support scientific cooperation even when diplomatic relations between the two countries were suspended.

Over the years, more than 4,000 students, scholars and artists have received scholarships to study or to carry out research at German universities and institutes, not only from the DAAD but also from the Alexander-von-Humboldt Foundation. In addition to scholarships paid for by Germany, the Egyptian government has sent hundreds of students to Germany. How attractive a German-style education is can be seen by the popularity of the three German schools in Egypt, where only about one in five applicants can be admitted, despite rising school fees. Egypt is also home to the largest 'export' experiment of German universities: the German University in Cairo, founded in 2003 under patronage of the Ulm and Stuttgart universities, already has more than 6,000 students. One of

the most important aims of the curriculum (and a 'unique selling point') of both German schools and German 'export' universities is not only to pass on knowledge, which can be memorized, but to inspire students to think for themselves.

Why, then, is science and technology in Egypt so unsatisfactory, especially compared with the more scientifically dynamic countries in the Far East such as India or China? While these countries have seen a tremendous leap forward, Egypt, like most other countries in the Middle East and North Africa (MENA) region, has stagnated, and some indicators suggest that the situation is getting worse. German researchers looking for international partners are turning away from Egypt to more promising countries in the Far East. To find out why, there are several factors we should consider.

Problems facing young Egyptian scientists

For a long time, German support has mainly been focused on training and educating Egyptian academics in Germany, without really considering what would happen when they return home. Too often, these well-qualified scientists are quickly disappointed because the research environment at their home institutions in Egypt is so different from what they experienced in Germany. They find a shortage of equipment and funding, and face difficulties posed by an extremely rigid hierarchical and seniority system that bases promotion (and funding) more on age than on scientific potential. There are, in short, many reasons why the promising career of a young researcher can come to an abrupt end. In addition, university work is very poorly paid, forcing them to look for second or even third jobs, often away from academia. So it is easy to see why Egyptian scientists perform quite poorly when applying for prestigious postdoctoral scholarships such as the programs of the Alexander-von-Humboldt Foundation.

If this analysis is correct, the young postdocs returning from Germany need much more support. The first 3–5 years after their PhD will determine whether or not the young researchers are given a chance to develop their potential. Of course, it is mainly up to Egypt to develop the academic environments where young researchers can prosper. The

first steps have already been taken, some of them (such as improving the quality of management) with support from international organizations like the World Bank.

But it is still not easy to see the light at the end of the tunnel. As Samia Farid Shihata wrote in *Al-Ahram*: 'The changes implemented obviously don't add up to an overall reform strategy capable of catapulting Egypt into a qualitatively higher plane of development.' However, the Egyptian President and government have recognized that things need to change, acknowledging 'a huge responsibility on us all to accelerate efforts to build the aspired knowledge society, to continue to encourage science and scientists to support scientific research and expand its base'. In the framework of a national strategic plan, a total budget of almost 1 billion euros has been made available to fund research activities; a new Supreme Council for Science and Technology, under the supervision of the Prime Minister, will create a more favourable political environment; and a process to identify centres of excellence for results-oriented funding is well under way.

Germany's role in Egypt's recovery

Nobody is expecting Germany to solve Egypt's problems, but German expertise and advice are generally welcome, if presented in an appropriate way. There are several areas where Germany can contribute.

Long-term scholarships for Egyptian students and graduates to Germany are still important, but constant contact with the home institution should be maintained. If this contact is lost, it can result in highly qualified graduates who can work well in Germany or the United States, but who are unable to cope with the Egyptian research environment. The focus needs to be on scholarships following the 'channel' model, where the least possible time is spent in Germany, where faculty members from both Germany and Egypt supervise the PhD thesis, and the final examination (and the awarding of the degree) takes place in Egypt. To cater for the needs of large numbers of students, joint funding is needed.

Specialized academic and scientific training should be supplemented by training modules in 'soft skills', covering all aspects of research management, cooperation with industry, teamwork and writing research proposals. Part

of this training should be included in the scholarship's scheme and offered (in the form of weekend seminars, for example) in Germany; the rest should be led by German bodies such as the DAAD or the Alexander-von-Humboldt Foundation. The DIES (Dialogue on Innovative Higher Education Strategies) training course on 'Proposal Writing', offered by the DAAD in cooperation with the Bibliotheca Alexandrina, is a good example. In addition, online and distance learning should be developed.

Consulting and training services should be offered to the senior management level of Egyptian universities, research institutes and the Ministry of Higher Education. For example, the independent selection procedures used by the German Research Foundation (DFG) for funding decisions are highly attractive from an Egyptian point of view. Here, and in similar cases, German institutions can help to shape the Egyptian research landscape.

Alumni activities mainly involve networking and help to keep people in touch. German funding institutions face the challenge of motivating Egyptian alumni to continue close cooperation with their German partners. New incentives are needed, such as training seminars, equipment grants and priority access to joint research funds. The topic should be discussed further and should seek to integrate not only DAAD and Humboldt alumni but also former government scholarship holders and self-paying students.

There should be a move from bilateral to multilateral cooperation. Increasingly, through its Framework programs, the European Union is becoming the biggest funding agency for international research cooperation. Egypt's future success in obtaining EU funding, which was quite disappointing under Framework Programme 6, will largely depend on the willingness of German and other EU researchers to carry out joint research work with their Egyptian colleagues. To this end, training in writing research proposals is needed. Private universities, often in close cooperation with well-known universities from Europe or the United States, are being set up in Muslim countries. Egypt is now home to not only a German university, but also a British, a French and a Russian university. Although private universities tend to have a bad reputation for just churning out degrees, they can also serve as a role model, especially for the close combination of teaching and research. This is the classic

'Humboldt model' of which Germany is so proud. The German University in Cairo is based on this idea.

Finally, there is the question of how to cooperate with industry. The topic is of the utmost importance, because currently less than 10% of research in Egypt is funded by private industry. Once again, this is a field where Germany has a lot to share, drawing on the experience of the Fraunhofer Society, for example. The German University in Cairo, which is following a strategy of close cooperation with industry in setting up a business park, might serve as an excellent starting point to further investigate the German model.

The German–Egyptian Year of Science and Technology in 2007 was based on some of these ideas.

The German–Egyptian year of science and technology

When Egypt's President Mubarak called for a 'decade of science years' in a bid to internationalize Egyptian universities and research institutes, he selected Germany as the first partner, paying tribute to its long-standing tradition of academic exchange and cooperation. What might have looked at first like a media stunt has turned out to be nothing less than a new start, building on firm ground prepared in the past.

The main idea of the Science Year (and the years to follow), as agreed between the German and Egyptian science ministries, was to reconnect Egyptian students and scientists to the international world of scientific and technological innovation. Realizing the international nature of today's scientific work, the project is aiming to integrate highly qualified young scientists into existing and newly created networks with German counterparts. As well as benefiting Egyptian scientists directly, this will strengthen the scientific infrastructure in their home countries, helping Egypt avoid the 'brain drain' that is already causing so many problems. This aim is very much in line with the recommendations of the *Arab Human Development Report* (2002): 'Benefiting from research and technological output depends critically on a robust system of national and international linkages among practitioners. Brazil, China and the Republic of Korea have established system linkages and policies in order to benefit from their national knowledge base.'

Networks have been created with an Egyptian and a German coordinator nominated by the ministries to cover six core areas of research cooperation: water, biotechnology, medicine, materials science, renewable energy and social sciences. With a budget jointly provided by the two countries, it was left to the coordinators to organize a series of conferences, workshops, summer schools and academic exchanges in order to set things in motion. A number of larger events (including a visit by the German research vessel *Meteor* to Port Said) were directed at the public to increase awareness of the importance of science and technology in today's world. Industrial partners have sponsored several small, cultural projects involving German schools and a children's project at the Coptic Museum in Cairo. On behalf of the German Federal Ministry of Education and Research, DAAD, in close cooperation with the German Embassy, acted as the coordination unit for the Science Year.

The Science Year gave rise to an impressive range of events, from small workshops to large conferences involving several hundred people. According to the calendar of events on the webpage http://www.yearofscience.org, the total number of events under the umbrella of the Science Year is close to 200. But it is not all about quantity. More much impressive is the new-found interest from Germany to cooperate in joint projects, and this interest can be seen in the large number of German researchers who came to Egypt and in the German institutions, such as the German Research Foundation (DFG) and the Alexander-von-Humboldt Foundation, which are increasing their cooperation with Egypt. The DFG, for example, has invited a delegation from Egypt's State Ministry of Scientific Research to Bonn to discuss the independent review and selection process for the distribution of research funding. The momentum created is quite impressive, but it must be both sustained and translated into action.

Perspectives for future cooperation

The slogan of the Science Year was 'Linking Scientific Masterminds'. This has been achieved, and the next step is to enable them to continue and expand their work by developing and presenting joint project proposals,

for example. This has led to the creation of various support measures. German and Egyptian representatives have agreed a new joint short-term scholarship program (GERSS), a PPP (a project-related exchange of personnel program, GESP) and an impressive long-term PhD scholarships program, enabling Egyptian scientists and their German partners to continue their work. But direct funding for research work is also needed, and the two sides have negotiated a joint research fund, which will provide joint research teams with start-up money for projects that can later be funded by the European Union through its next Framework Program, by other international organizations or by national funding bodies, such as Germany's DFG. A training course on writing scientific proposals has been organized by the DAAD, with funds from the Ministry of Economic Cooperation and Development, and this was offered at the Bibliotheca Alexandrina in two parts in 2007 and 2008.

9

A Decade of US Support for Agricultural Biotechnology in the Developing World

Frank A. Shotkoski

In many developed countries, genetically modified crops already contribute greatly to agricultural productivity and sustainability. Over the past few years, the largest growth in the use of genetically modified crops has been in developing countries, and this trend is expected to continue (James, 2007). Multinational life-sciences companies have led the way, but they have focused primarily on a few combinations of crops and traits that have high commercial value and serve large international markets. Because of the costs and complexity of the issues related to crop biotechnology, many crops and traits that are important to subsistence and resource-poor farmers have been overlooked.

The Agricultural Biotechnology Support Project (ABSPII), a consortium of public- and private-sector institutions led by Cornell University and funded by USAID, is filling the gap, providing support for scientists, regulators, extension workers, farmers and the general public in developing countries to make informed decisions about agricultural biotechnology. Where demand exists, ABSPII works with local institutions to establish safe and cost-effective programs for the development and commercialization of genetically modified crops that otherwise would not be developed. Where possible, ABSPII creates public–private partnerships to help leverage both public and private funding sources to absorb the development costs and provide broader distribution channels. ABSPII is currently working in

India, Bangladesh, the Philippines and Uganda to develop products with the intention of reducing poverty and alleviating hunger. Here I discuss the strategy taken to develop and deliver genetically modified crops to developing countries and describe examples of several ABSPII projects.

A demand-driven strategy

ABSPII is designed to complement national and regional efforts to develop and commercialize safe and effective genetically modified crops in developing countries. ABSPII puts a high priority on identifying and delivering products that address important food-security issues for each participating country. Priority-setting consultations are conducted at an early stage with local stakeholders to ensure that they are happy with the proposed projects. The primary objective is to avoid investment in technology that is unlikely to be adopted. The priority-setting exercise is supported by economic studies performed by experts in research evaluation and socio-economic analysis. The process considers all of the key technical and non-technical components that affect farm-level acceptability and productivity among female and male farmers, and balances country-specific, regional and even global needs.

ABSPII and its partners select products that are likely to have a significant positive socio-economic impact and for which there is strong demand by local stakeholders. This results in a higher degree of acceptance and inspires leaders in the focus countries to develop the political will required to leverage national financial support. It also provides the motivation necessary to implement policies that promote the testing and eventual commercialization of the product.

All project implementation phases from product selection to marketing and delivery are conducted in the context of a product commercialization package (PCP) approach that integrates every element of the research, development and commercialization processes. The main elements of each PCP are illustrated in Figure 1 and include:

- Technology development
- Policy-related issues, such as licensing the intellectual and technical properties associated with the product, as well as applying for and obtaining regulatory approval from the relevant national authorities

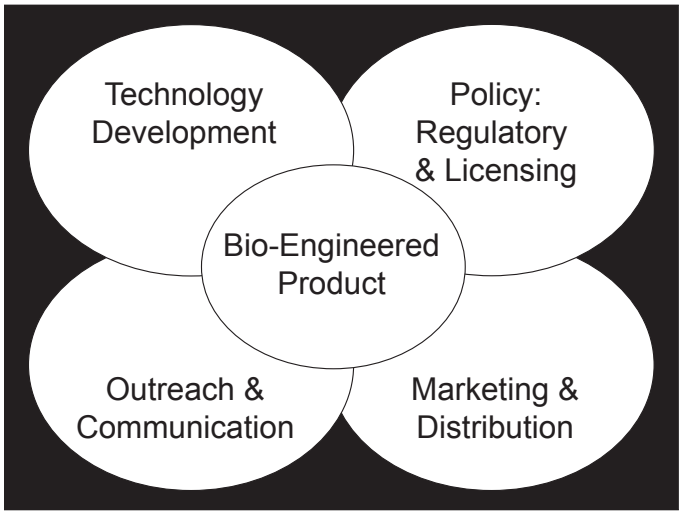

Figure 1 The main elements of an integrated product-driven approach to the research, development and delivery of genetically modified crops. Source: ABSPII.

- Communicating public information to producers and consumers about the benefits, risks and correct management of the product
- Establishing or verifying the existence of marketing and distribution mechanisms to provide farmers with access to planting material (Gregory et al., 2008)

The specific activities that occur within each quadrant of Figure 1 depend on the nature of the particular genetically modified crop being addressed. It should be noted that there can be considerable differences in the specific research, development and delivery issues associated with different products and locations. For some products, technology development might be the primary focus. For others, product development work might be complete, and issues related to policy, communication and outreach, or marketing and delivery mechanisms may be of primary concern. In countries where genetically modified crops are already approved and some are already in use, the emphasis is placed on the commercial delivery of products, either through private companies or efficient public-sector systems. In countries with little or no experience in evaluating genetically modified crops, the focus may instead be on strengthening product-development expertise and sourcing existing products for field trials.

Building a team

Project implementation starts by building a team of people and organizations with the skills and experience to adequately address every stage from product selection to commercialization. These teams often include national and international bodies, and in many cases include private companies that have experience in conducting product development, commercialization and distribution activities that ensure delivery to the end-user. The private sector also has much to offer developing countries in terms of strategic research (for example, in genomics, bioinformatics and bioengineering) and, depending on the circumstances, can provide technology or knowledge for goodwill or for a share of the profits.

Capacity building

Most human-resource and infrastructure capacity-building initiatives in developing countries have concentrated on basic research. ABSPII focuses instead on building capacity in areas associated with product development, commercialization, marketing and distribution of genetically modified crops. These activities are broad in nature and complex, so it is also necessary to put considerable effort into building capacity in the areas of policy development, regulation, intellectual property rights and communication. When possible, ABSPII provides practical, real-life experiences for scientists and technicians, farmers, communication and outreach specialists, media personnel, risk-assessment managers, policy makers and others.

Most of the technologies associated with genetically modified crops have been discovered and developed by the private sector. Private-sector companies usually own their intellectual property or have negotiated the right to use the technology. The public sector is still learning how to deal with intellectual property rights (IPR). The public sector, especially in developing countries, often lacks trained professionals with the experience to understand IPR issues and with access to clear policy and institutional support for IPR from senior management. ABSPII works with partners to address the management of IPR by raising awareness of its importance and stressing the need for the implementing organizations to develop clear procedures for handling materials and licences.

Many ABSPII projects are in the product development phase, so it is necessary to obtain governmental approval for field trials to test the technologies under natural conditions. ABSPII has been successful in building capacity in several critical areas needed to gain approval for field trials. These include facilitating dialogue among those responsible for setting national biosafety standards and promoting policy linkages in sectors affected by a particular product; providing support for the implementation of effective national biosafety mechanisms; strengthening capacity in biosafety risk assessment, risk management and biosafety communication; and enhancing capacity in public awareness and advocacy. ABSPII works closely with another USAID-funded project, the Program for Biosafety Systems, on policy-related issues.

Acceptance and market access for genetically modified crops is dependent on the attitudes of stakeholders such as local scientists, regulators, journalists, extension workers, farmers, retailers, religious groups and consumers. Transparent information about the technology needs to be disseminated in a way that builds understanding and trust among all the stakeholders so they can make informed decisions. ABSPII has a solid communication strategy that provides sound science-based information on its genetically modified products to stakeholders and policy makers.

A responsible marketing and distribution system needs to be in place, or at least be planned, early in the project. ABSPII has adopted a policy of establishing the early involvement of downstream partners, particularly private-sector suppliers of seed and other agricultural products. Seed distributors, private or public, need to have the capacity for product stewardship policies to maximize the benefits and minimize any risk from using the product.

ABSPII-Supported products

ABSPII is currently working on projects in India, Bangladesh, the Philippines and Uganda. Now I will provide a brief description of several specific projects and the strategy ABSPII has taken to develop and deliver genetically modified crops.

Bt Eggplant in South and Southeast Asia

In South and Southeast Asia, eggplant is an economically and nutritionally important crop and a staple of human consumption. Its cultivation helps to generate valuable income for farmers and labourers. However, the production of marketable eggplant is seriously compromised by the numerous pest species that feed on it, especially the eggplant fruit and shoot borer (EFSB), *Leucinodes orbonalis Guenée*. The larvae bore into the terminal shoots, causing the plant to wither. The pest also bores into the fruit, making the fruit unmarketable. Infestation can result in the loss of 70% of the crop and damage 90% of the fruit (Dhandapani et al., 2003; Baral et al., 2006). Nearly all farmers rely on multiple applications of chemical insecticides to combat EFSB. This practice has resulted in the widespread misuse of pesticides, with a multitude of consequences including increased cost of production and overexposure to pesticide residue for farmers and consumers. The excessive use of chemical pesticides also kills the natural enemies of EFSB, resulting in a resurgence of the pest's population.

No conventionally bred resistance to EFSB is available, and attempts to cross eggplant varieties with EFSB-resistant wild varieties have been unsuccessful. For this reason, ABSPII explored the possibility of developing and marketing eggplants containing a Cry1Ac transgene obtained from the soil-borne bacterium *Bacillus thuringiensis* (*Bt*) that provides resistance to EFSB. A major advantage of this technology is a reduction in the use of chemical pesticides, thereby reducing production costs and minimizing environmental risks.

An ABSPII priority-setting exercise was conducted with local representatives of public- and private-sector stakeholder groups from India, Bangladesh and the Philippines. Given the potential benefits of the technology, the *Bt* eggplant project was assigned a high priority. This was not only because of its verified technology and potential economic, health and environmental benefits, but also because of the absence of obstacles in terms of intellectual property rights, along with favourable prospects for regulatory approval, a high degree of expressed interest from strong local partnership organizations, and a high likelihood of gaining public acceptance for the product given its positive socioeconomic implications (Kolady and Lesser, 2006).

ABSPII, in cooperation with Hyderabad-based Sathguru Management Consultants, worked with the private seed company Mahyco to devise a system whereby all farmers could gain access to the FSBR technology. In India, Mahyco will profit from the technology by selling *Bt* eggplant seeds to farmers currently engaged in cultivating hybrids. Meanwhile, the public–private partnership will allow public institutions to give resource-poor farmers access to high-quality open-pollinated genetically modified seeds at the relatively low cost of seed production and distribution.

In the Philippines, most farmers purchase and cultivate hybrid eggplant. In addition to private enterprises such as the East-West Seed Company, the University of the Philippines at Los Baños (UPLB) is engaged in delivering hybrid seeds to resource-poor farmers through its seed production unit, UPLB's Institute for Plant Breeding (IPB-UPLB). Appropriate licensing agreements will be negotiated with commercial seed producers who may help to distribute the *Bt* eggplant.

In India, public partners include the Indian Institute of Vegetable Research, Tamil Nadu Agricultural University and the University of Agricultural Sciences in Dharwad. In Bangladesh, the main public partner is the Bangladesh Agricultural Research Institute (BARI), which has developed numerous eggplant varieties. The primary private-sector partner is the East-West Seed Company, a multinational vegetable-seed producer with a market position in all the major Southeast and South Asian vegetable seed markets. All the institutions and private enterprises that work with ABSPII on this project were selected because they have the capability and infrastructure along with a strong track record for responsible seed development and multiplication for distribution to end-users.

In all three countries, the public institutions have carried out field trials to assess the efficacy of the technology against EFSB and to generate the biosafety data necessary to develop a regulatory dossier. The field-trial approval process is different in each country, but legislation and policies that allow the trials to be done in them all exist. ABSPII makes the field-trial applications and conducts the field trials based on the recommendations laid out by the relevant national regulatory system. India, as the primary recipient and developer of the *Bt* eggplant technology, has generated sufficient biosafety and food-safety data for potential approval by the

Genetic Engineering and Approval Committee for the commercialization of *Bt* eggplant. More than 1,000 pages of regulatory data generated by Mahyco in India are now posted on the Internet and are available to the public for further comments and suggestions.

ABSPII has promoted further collaboration among the three participating countries in terms of regulatory file preparation and biosafety.

Participating researchers from Bangladesh and the Philippines have received training from the Indian partners in aspects of regulatory science. The Indian partners have also shared relevant data with Bangladesh and the Philippines to expedite field trials and product evaluation involving both biosafety and food-safety tests. Such South–South collaboration not only reduces costs but also enables the exchange and use of relevant regulatory data to address local needs. This approach is now being promoted by ABSPII in all its other PCPs.

Late-Blight-Resistant Potato in South and Southeast Asia

Potato is an important vegetable crop for resource-poor farmers in India, Bangladesh and Indonesia. It is a highly nutritious food that provides many essential vitamins, minerals and amino acids, and is an important supplemental source of nutrients and calories for people living on a rice-dominated diet. Unfortunately, the fungus *Phytophthora infestans,* which causes a disease called 'late blight', is threatening potato cultivation in South and Southeast Asia and threatening food security in the region. Late blight occurs worldwide and spreads extremely quickly. An entire crop can be destroyed within one to two weeks, depending on the weather. Controlling this disease is essential for resource-poor farmers who depend on potato for basic nutrition. Farmers who can afford fungicides apply them repeatedly and often excessively, creating serious environmental and health risks and greatly reducing their profits.

Fortunately, a close relative of the potato, *Solanum bulbocastanum*, has a naturally occurring set of genes that provides high levels of resistance to late blight. Attempts to cross these genes into domesticated potato varieties using conventional breeding techniques have been unsuccessful. A major late-blight resistance gene, RB, has been isolated from *S. bulbocastanum* and researchers at the University of Wisconsin have successfully transferred the gene into a commercial potato variety known as Katahdin (Song et al.,

2003). Preliminary data from field trials suggest that expression of the RB gene in genetically modified potatoes significantly reduces the incidence of late blight and the need for multiple fungicide applications.

If RB technology were to be a demand-driven commercial product that would fit the PCP model, it would have to be capable of reducing fungicidal use by at least 30%. The data suggested that RB technology would not only meet but exceed this requirement. ABSPII and its partner Sathguru Management Consultants brokered a licensing agreement from the Wisconsin Alumni Research Foundation that allows ABSPII's partners to conduct experiments to assess the efficacy of the RB technology against regional strains of P. infestans. ABSPII established a consortium comprising researchers from the Central Potato Research Institute (CPRI) in India, BARI, the Indonesian Vegetable Research Institute (IVEGRI), the Indonesian Center for Agricultural Biotechnology and Genetic Resources Research and Development, the University of Wisconsin and Cornell University to use the RB gene in South Asia.

Two genetically modified versions of the potato cultivar Katahdin were provided to the consortium partners by the University of Wisconsin and evaluated in a limited field trial at Shimla, India, by CPRI and at Lembang in Indonesia by IVEGRI. Both versions provided a high level of field resistance to Indian and Indonesian isolates of P. infestans. CPRI and BARI have begun transformation work with the RB gene to introduce it into locally acceptable germplasm. As a back-up, CPRI has established a conventional breeding approach to develop new late-blight-resistant cultivars. Similar research and product development activities are being conducted in Bangladesh and Indonesia.

The East African Highland Banana in Uganda

The East African Highland (EAH) banana, known locally as matooke, is one of the most important food and cash crops in Uganda, as measured by production output, acreage, consumption levels and priority ranking by stakeholders (Kikulwe et al., 2008). During the past thirty years there has been a drastic decline in production in the traditional banana-growing areas of central and southwestern Uganda. According to Uganda's National Agricultural Research Organization (NARO), the most serious constraints to banana production are black sigatoka, nematode and weevil

infestation. Black sigatoka alone can reduce yields by 30–50% and the disease affects all traditional banana cultivars in West and Central Africa and most of the widely grown cultivars in Eastern Africa. In addition, several nematode species attack banana in Uganda. Cumulative yield losses attributed to nematodes can reach 51% by the fourth crop year. Almost all EAH banana varieties are also susceptible to attack by banana weevils, which can result in crop losses of up to 100%.

Conventional banana breeding relies on crossing cultivated triploids with wild relatives, followed by extensive backcrossing. This is a long, laborious and often unsuccessful process. Genetic modification offers the possibility of moving desirable traits into acceptable banana germplasm in a more precise and timely manner.

The first task for ASBP II was to work closely with management and researchers at NARO to revamp their research strategy and to prioritize the activities to be carried out by the consortium of partners involved. The project partner institutions included the Katholieke Universiteit Leuven (KUL), the University of Leeds, Cornell University and NARO. ABSPII provided the technical oversight and support to oversee the design of a state-of-the-art banana tissue-culture laboratory, the building of a research team with the skills to develop a reproducible transformation system, and the capacity to develop and test genetically modified bananas. More recently, ABSPII facilitated the construction of a containment greenhouse facility and confined field-trial site at the National Agricultural Research Laboratories Institute (NARLI) in Kawanda, Uganda.

Initial priority-setting exercises established that the technology was available for improving the resistance of EAH bananas to black sigatoka and nematode infestation. Although the banana weevil is a significant pest, no insecticidal protein technology was available for consideration. For black sigatoka resistance, an antifungal chitinase gene from rice was transformed into a Gros Michel banana at KUL by a Ugandan scientist who has since returned to NARO to continue his work on developing improved gene transformation systems and applying them to EAH bananas. For nematode resistance, EAH bananas were transformed with a maize cystatin gene at the laboratory in Uganda. Several independent genetically modified bananas have been generated and will soon be tested under greenhouse and contained field-trial conditions.

In August 2007, genetically modified banana plants carrying the rice chitinase gene were imported to Uganda from Belgium. After a hardening period, they were planted in a confined field trial at NARLI in November 2007. The field-trial application and approval process in Uganda was a significant capacity-building exercise for NARO. It took nearly two years to complete, but much was learned, and it is anticipated that future application processes will be handled more effectively. It is also anticipated that new policies and legislation will soon be adopted in Uganda that will allow the commercialization of genetically modified crops.

PRSV-Resistant Papaya in the Philippines

Papaya is one of the most economically important and nutritious fruits in the Philippines. It ranks sixth in production and fifth in volume among fruit crops in the country, and is grown primarily by small-scale farmers. Unfortunately, papaya cultivation in the Philippines is severely constrained by several diseases and pests, the most widespread and destructive of which is the Papaya Ringspot Virus (PRSV). PRSV has decimated commercial papaya cultivation in Southern Luzon. There are no consistently effective conventional management or control measures against this devastating disease, and no naturally occurring sources of resistance are available. But genetically modified papayas using virus coat protein technology developed by Cornell University and the University of Hawaii have been demonstrated to provide highly effective control of PRSV, and are responsible for the revitalization of the papaya industry in Hawaii, USA.

Through an initiative of the Department of Science and Technology, a partnership between the Philippine Council for Agriculture, Forestry and Natural Resources Research and Development, IPB-UPLB and Monsanto, a local Philippine variety was made resistant to the virus by genetic modification. The International Service for the Acquisition of Agri-Biotech Applications (ISAAA) gave technical assistance and oversaw the technology transfer from Monsanto to the Philippine partner institutions. With assistance from ABSPII and its partners, IPB-UPLB has made significant advances in the development of PRSV-resistant papaya. From primary genetically modified plants generated in 2002, candidate lines have been selected and advanced several generations. The candidate

papayas are currently being assessed for efficacy in a confined field trial in the Philippines.

Conclusions

ABSPII and its partners are taking bold steps to introduce genetically modified crops as a mean of providing solutions to important and previously intractable problems facing subsistence and resource-poor farmers in the developing world. The progress made has not come without frustration, however. The complexity associated with the use of genetically modified crops is vast, and working through regulatory processes, archaic and prohibitive policies, legal wrangling and bureaucracy has been a challenge. The strategy used by ABSPII has been quite successful and might be considered by others as a framework, or at least a starting point, for building the capacity of developing countries to safely and effectively develop and us genetically modified crops, especially for crops that are of little business interest to the large multinational biotechnology and seed companies.

The *Bt* eggplant produced for South and Southeast Asia is the most advanced ABSPII PCP. We expect the product to be deregulated in early 2009. Seed from the public sector should be available 6–12 months after Mahyco commercializes the hybrid seed. The other PCPs highlighted above—the virus-resistant papaya, the disease- and nematode-resistant banana and the late-blight-resistant potato—are all making good progress and should be commercialized in their respective countries. In each case, the advances in technology and communication to improve consumer awareness and the acceptance of genetically modified crops will benefit the poor and hungry. Such advances would be impractical using conventional plant breeding or non-breeding approaches.

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10

New Roads for Technology Transfer in Sub-Saharan Africa

Cynthia P. Schneider

> 'In another era, a nation's most valuable assets were its natural resources—coal, say, or amber waves of grain. But in the information economy of the 21st century, the most priceless resource is often an idea, along with the right to profit from it. This reality is transforming business and creating new diplomatic fault lines between continents.'

This quote from the *International Herald Tribune* (2005) seems to offer hope for developing countries, as ideas have no geographical boundaries. However, developing countries often lack the ability to put ideas into practice.

Here I will address the challenge of translating the ideas developed in the laboratories of sub-Saharan Africa's agricultural research institutions into products. Accomplishing this goal requires not only sound and efficacious research, but also an entrepreneurial business climate with the conditions —intellectual property and regulatory structures, effective and transparent financing conditions, and access to markets—in which new products can be developed, sold and marketed.

The knowledge of scientists in both the developed and developing worlds is an asset that can lead to economic development, jobs (financially and intellectually rewarding positions for top scientists) and essential

products for farmers. However, making this happen is dependent on the existence of translation mechanisms to foster the commercialization of research. Establishing the means and mechanisms to develop agricultural technologies that increase yield or that grow value-added products could benefit small-scale farmers in Africa, say, potentially enabling them to move from subsistence to revenue-producing farming. The commercialization of these technologies would provide skilled jobs for scientists and engineers, enabling them to earn revenue from their knowledge. In the long term, these opportunities could help provide incentives to retain an educated workforce in Africa and to stem the brain drain.

Commercializing agricultural technologies could provide opportunities for people at different income levels–farmers, scientists and investors–to make money. This would reduce Africa's dependence on aid, increase standards of living, stem the exodus of the well educated, and may even, over time, precipitate changes in the financial, regulatory and legal sectors to improve the climate for entrepreneurship, business development and technology transfer.

Public–private partnerships are essential to achieving these objectives. The most successful partnerships are likely to be those that are integral to the strategic plan of the private partner (as opposed to short-term public relations). The partnership must also deliver a core benefit to the consumers, who in this case are small-scale farmers. If benefits accrue to the private partner as well as the public partner and the consumers, the project has a greater opportunity for sustainability.

In the next five-to-ten years, the research that has been carried out in African universities and public-sector research institutions, such as the Kenya Agricultural Research Institute and the National Agricultural Research Organisation (NARO) in Uganda, will bear fruit. Products such as cassava that is resistant to the African cassava mosaic virus, bananas that are resistant to the fungal disease black sigatoka, and a vaccine to combat the cattle disease East Coast fever will be ready for trials and eventual commercial release. But several roadblocks stand in the way of these and other products that can improve the yields and lives of African farmers. Regulations must be in place before biotechnology products, such as the mosaic-virus-resistant cassava developed at NARO in Uganda, can be released.

Countries that already have regulations in place, such as Kenya and South Africa, still face the challenge of translating scientific innovations into businesses. Even the United States and Europe struggle to develop businesses from the intellectual property of public-sector institutions. In Africa, there is no entrepreneurial sector or climate, and many of the accompanying components, such as venture capital, transparent financial institutions, legal and intellectual infrastructure, favourable bankruptcy laws, tax incentives, entrepreneurs and a trained workforce, are lacking. As a result, the research is stuck in the institutions, rather than being developed into businesses and products that can reach the farmers who need them. As Debby Delmer, then of the Rockefeller Institute, explained: 'What seem to be lacking are systems that promote and reward efforts to create a strong interface between fundamental and applied research in support of global agriculture.' (www.pnas.org/cgi/doi/10.1073/ 10.1073/ pnas.0505895102). How can this problem be overcome?

A virtual incubator

At a meeting in October 2005 supported by the Rockefeller Foundation, and held at the Foundation's Bellagio Center in Italy, participants developed a concept to address the challenges of translating research and technology transfer in Africa, with a focus on sub Saharan Africa. Drawing on examples of successful technology transfer from Bangalore, Ireland, Georgetown University and the Washington DC Board of Trade, and building on lessons from the pharmaceutical and agricultural industries, the Bellagio group developed the concept of a 'virtual incubator' to both fund and mentor technology transfer and business development projects.

The concept was inspired by a successful virtual incubator developed in Washington DC, which dramatically increased product development and revenue to universities. Technology-transfer officers worked with the Washington Board of Trade to develop a system to pool promising research from local universities and have it vetted by venture capitalists. Those projects judged ready for financing and development then made a formal presentation to a larger group of potential investors. This multi-step process allowed investors to see research at an early stage, secure

in the knowledge that the presentations reflected research that has been vetted, and gave scientists increased access to venture capitalists as well as mentoring and advice at various stages of their research.

This model would have to be altered to fit the needs of sub-Saharan Africa and its technologies, but the basic concept of a group to mentor and fund technology transfer would remain. Such a virtual incubator in the developing world should include investors, business experts and industry representatives, scientists, government representatives, lawyers and intellectual-property experts. The group could both solicit projects in Africa and look for research that is ready for development. Projects would be selected on a competitive basis. The virtual incubator then would bring in capital and mentor the project at every stage of business development.

The goals of the virtual incubator would be to capitalize on research in agricultural technologies that address problems facing small-scale farmers, and to facilitate the commercialization of those technologies. Translating the technologies into products will help both small-scale farmers and scientists. The farmers will benefit directly from the technology, and the scientists can use it to generate revenue for themselves and the community. Key elements for success include identifying market-driven opportunities, establishing viable public–private partnerships, and ensuring the sustainability of the existing industrial base.

The JKUATES project established by Nick Wanjohi, Vice-Chancellor of Jomo Kenyatta University of Agriculture and Technology in Kenya, provides an example of the successful commercialization of university research. Established to act as link between university and industry, JKUATES has successfully commercialized food products, software, cosmetics and solar heaters, among other products.

The benefits of developing agricultural products are enormous, but the challenges are daunting. One alternative is to use the virtual incubator to develop health products. As Evans Taracha of the International Livestock Research Institute explained at the Bellagio meeting: 'There is still a debate going on in Africa about whether public/private partnerships can deliver public goods through advanced technologies in agriculture. This debate never has existed in the health field: vaccines have been among the greatest public goods of the 20th century.' Anatole Krattiger pointed out that

health products are more likely to have a guaranteed market, even if it is an international organization such as the World Health Organization, whereas agricultural products rely more on individual consumers, adding that the successful commercialization of agricultural products also depends on a viable infrastructure for delivery.

Putting Theory into Practice

The virtual incubator mechanism can be used to develop a wide range of products, including:

- Cassava for food, starch and energy production
- Plant-derived biomaterials and industrial products
- Plant-derived vaccines and pharmaceuticals
- Biofuels (ethanol from corn or cassava)
- Biomass for energy production
- Tissue-culture businesses (these could work in conjunction with improved plants, such as mosaic-virus-resistant cassava or bananas resistant to black sigatoka, or to develop exotic fruits or flowers)
- Medicinal plants and derived products
- East coast fever vaccine

Market-driven pilot projects with sound business plans stand the best chance of attracting investment. In the case of public–private partnerships, the project is more likely to succeed and achieve sustainability if it aligns in some way with the core business of the private partner. Given the worldwide energy crunch, a biofuels project would seem promising, but this field has been complicated by the 'food or fuel' debate. South Africa has a government policy supporting biofuels, and a commercial biofuels venture was launched there a few years ago.

Conclusions

The challenges of translating research into products are great in both the developed and the developing world. But it would be a tragedy if the products developed specifically to address the dire agricultural needs of sub-Saharan Africa were allowed to languish in the laboratory. Years, if

not decades, of investment in research and training African scientists have yielded impressive results in the laboratory, but science alone cannot deliver the products into the hands of farmers. Achieving that goal requires legal, regulatory and commercial infrastructure, as well as an entrepreneurial climate that values creativity and encourages risk-taking. The 'virtual incubator' mechanism brings together investors, licensing experts, scientists, local government officials and lawyers to jumpstart the process of technology transfer. It could help to accelerate the process of delivering improved agricultural products into the hands of the farmers.

Acknowledgements

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11

Building Research Capacity Through the 'Supercourse'

Faina Linkov, Francois Sauer, Eugene Shubnikov, Ronald LaPorte

Developing countries, especially in the Islamic world, are facing a growing threat from non-communicable diseases (NCDs). The use of drugs and vaccines saw their populations rise before levelling off (the 'epidemiological transition'), but they now face the twin burden of both infectious and chronic diseases. Part of the problem is that developing countries lack the scientific expertise to help them tackle such diseases. But how poor is their research base in this area, and how can it be improved?

Status of research in developing countries

Publications in NCD epidemiology are one metric of research productivity. We searched PubMed and Google Scholar for articles about diabetes epidemiology, cardiovascular epidemiology and cancer epidemiology dating from 2003 to 2007 for the 53 lowest-income countries, excluding clinical articles and those where the first author was from a developed country. We found just 474 NCD research epidemiology publications—a total of about 89 per year for the 53 developing countries. By contrast, the estimated number of articles published on NCD epidemiology globally during that period was 46,250. So only 1% of articles on NCD epidemiology come from developing countries, even though these countries suffer the most deaths from chronic disease. We plan to at least double the number of NCD publications.

Why are there so few scientific publications?

We examined the lack of scientific publications from developing countries in 2001 (http://clinmed.netprints.org/cgi/content/full/2000010008v1). About 25% of the world's scientists live in developing countries, even though these countries are home to 75% of the world's population, so the number of scientists in the developing world is far too low. But the situation is even worse than this, as can be seen from statistics provided by the editors of the BMJ (Figure 1). Given that developing countries are

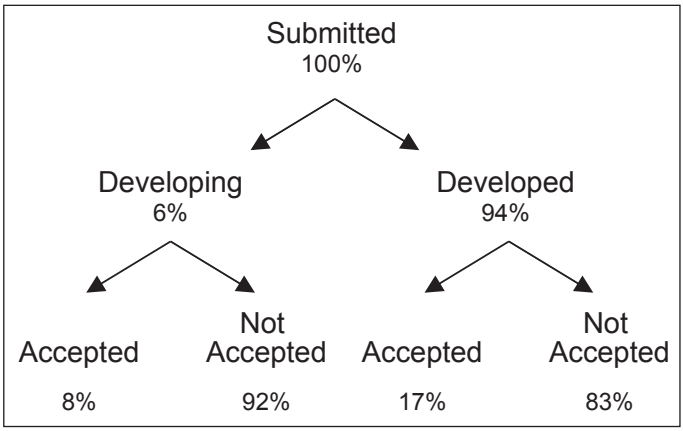

Figure 1 Submission and Acceptance Rates for Papers Submitted to the BMJ from Developing and Developed Countries.

home to 25% of the world's scientists, yet these account for only 6% of papers submitted to the BMJ. In addition, the acceptance rate was twice as high for authors from developed countries.

We have devised a program, known as 'Supercourse', that will increase the number of researchers who can carry out NCD epidemiologic research by upgrading NCD research skills and mentoring, double the number of NCD epidemiology papers submitted by authors in developing countries, and improve the quality of these papers.

Why Islamic countries?

There are 1.2 billion Muslims in the world, yet there is little collaboration between scientists in Muslim countries and those in the United States. We could find only four grants from the US National Institutes of Health (NIH) targeting the 57 countries in the Organization of the Islamic Conference (OIC). In addition, the rise of NCDs in Muslim countries has been rapid, unexpected and largely unexplored. Research in the Islamic world aimed at preventing disease was the best in the world 500 to 700 years ago, but now it has fallen on hard times. Evaluating the rapid rise of chronic diseases in OIC countries can show Western nations how their pattern of diseases developed. For example, we are seeing the widespread use of water pipes, such as hookah, nargile and shisha pipes in the United States. There is insufficient US data on the increased risk of cancer, cardiovascular disease, stroke and respiratory disease from smoking these pipes, as the duration is too short. However, in Egypt, Lebanon and elsewhere, many people have used water pipes for much longer.

The Supercourse program will act as a form of diplomacy and will help build a healthy research relationship between the United States and Muslim countries. We are confident about our ability to do this because more than 1,500 faculties from Islamic countries are already collaborating with us.

Why are so few people trained in NCDs?

Until now there have been very few NCD research classes in OIC countries, and many libraries in developing countries have no scientific journals less than 15 years old. It is difficult to teach new topics, such as NCD epidemiology, without the necessary training or materials. One option is to send students to the United States for training, although this is costly and can lead to 'brain drain'. A second option is for US researchers to teach in developing countries. However, few US scientists want to spend a year in the Sudan when they have careers at home.

We offer a third approach, the Supercourse Educational Model, in which we empower educators in Sudan for example by giving them

PowerPoint lectures to help them teach about NCDs and research. We have already demonstrated the power of this approach in many other low-income countries. With the Supercourse, lectures dramatically improve, yet local educators still have complete control over the content they are teaching. We plan to network potential teachers of NCD epidemiology in OIC countries and provide them with state-of-the art, certified NCD curricula. There will then be a rapid dissemination of the teaching about disease prevention and a marked improvement in teaching standards, as educators will be using materials provided by global experts. As proof of concept, last year our lectures taught more than a million students. We built a network of academic faculty and a library of lectures on the Internet, and thousands of teachers and students from developing countries came. College educators in low-income countries want to have up-to-date materials and give the best possible education to their students, but the burden of teaching a new topic without modern materials is too high, hence the infrequent teaching of NCD courses. But with access to slides and lectures from leading researchers (discussed further below), the quality is exceedingly high and current. Educators in developing countries can stand on the shoulders of giants and find it easy to teach about NCDs.

We need to build a sustainable training program within the existing educational framework in large universities, especially in low-income countries, by giving faculty the best possible slides, lectures courses, research skills and standardized testing, as well as a global mentoring service. We will also teach the faculty how to teach research.

The traditional approaches for workforce development in global health used by the NIH, World Health Organization, UNESCO and United Nations have been expensive without a very high throughput. Students from developing countries come to the United States for a PhD, for example, but only half return home. It takes at least US$100,000 to train one person to get a masters degree in public health (MPH). Even if an institution trained ten new MPH students a year, this would be only one MPH for every 100 million people. The United States produces one public-health graduate for every 40,000 students a year. Instead, we will train 400 researchers at a cost of only $2,500 each.

We have already demonstrated that the Supercourse is effective in teaching NCD research in developing countries by training thousands of

students. Supercourse is a grassroots model. By teaching the teachers, in their own country, we will train at least 400 students by building an NCD network, collecting lectures, sharing these lectures, and building what might be dubbed a 'research training curricula in a box'. In addition, we will establish standardized, inexpensive, global NCD projects based on the WHO and other low-cost international projects. At the same time, we will develop, with global experts, a five-course, 15-credit curriculum for NCD Supercourse Training. Students in Supercourse Training will be networked, as will all faculty members involved in the program. Networking will be local to global. After the completion of the program, there will be continued networking and encouragement for both faculty and students. We have already established the backbone of the curriculum in our Supercourse (www.pitt.edu/~super1/globalhealth/gh.htm).

The concept is simple: we establish a Global Non-Communicable Disease Supercourse to markedly improve NCD teaching and research in OIC countries by improving faculty lectures, building a global faculty mentorship program, and developing simple, inexpensive, chronic-disease projects based in part upon the WHO. Our target will be to foster the best teachers and the best interdisciplinary students at the best national universities.

How can we grow NCD epidemiologic projects globally?

Our approach for building capacity in OIC countries is based in part on our successes in training more than 500 people worldwide in diabetes epidemiology as part of the WHO Multinational Project for Childhood diabetes (WHO Diabetes Mondiale, DiaMond). This is a similar approach to that taken with the international training programs run by the Centers for Disease Control and Prevention. Ronald LaPorte started this project in 1990 and it continued for ten years. The project built type 1 diabetes registries worldwide to assess the geographic variability of the disease. The main finding was a 400-fold variation in incidence between Finland and certain areas in China. During the course of the program there were 155 centers from 70 countries with the Pittsburgh WHO Collaborating Center as the hub. A template registry of methods of operation was developed and provided to all the centers. To join, a center needed to develop its

own local protocol based on the template and have it approved by the experts. In addition, more than ten DiaMond training sessions were held with more than 300 students.

The WHO DiaMond project was an enormous success. It helped build a cadre of global diabetes epidemiologists. Before 1985 there were no registries and very few, if any, type 1 diabetes epidemiologists in developing countries. After 1990 there were 30 registries in 20–25 developing countries. There were approximately 100 investigators participating in the WHO DiaMond project from developing countries. Before 1990 there were no publications on the incidence of childhood diabetes in developing countries. After the beginning of the WHO project, 47 centers from 30 developing countries reported incidence data. These epidemiologic publications were about the largest number for any multinational NCD project. The trainees continue to publish.

We have been very successful in collaborating with OIC and low-income countries in the area of diabetes. We have collected and compared data for 21 Muslim countries using our WHO DiaMond Protocol. We have helped map out the incidence of type 1 diabetes in Muslim countries. We are confident we will be just as successful for other chronic diseases. The WHO DiaMond Project ended in 2000; however, many of the centers in Arab countries, and worldwide, which are supported by local sustainable interest, continue to this day.

We published more than 60 collaborative papers with scientists from Arab and Muslim countries. Most of the articles had first authors from low-income countries. The traditional NIH approach for collaboration with developing countries has been the infusion of significant funds from the United States for multiple different projects. This is difficult to sustain because the projects stop when the NIH funding ends. Our approach with funding will be the development of a small number of important, but simple and low-cost, epidemiology implementation projects that can inexpensively be completed in many countries. Our goal is to develop projects, such as the WHO DiaMond project, that are sustainable after the NIH money dries up. To do this, we create template protocols for a project that might include the registry monitoring of multiple NCDs, international behavioural risk factors, obesity and NCDs, for example. After the WHO DiaMond project, diabetes registries in developing countries have been

used extensively for many other studies, such as virology and molecular epidemiology, and most are still viable. Our WHO project was joined by 155 centers, even though it was not supported by the NIH.

A model of this sort builds a network of scientists worldwide that can be used as a support group. In addition, the populations can be used for years to come for many different research projects. In addition, the reference centers can help all the other centers.

We propose to develop a similar model, in part built upon WHO and CDC multinational projects. Remember, we have had considerable experience in successfully training scientists and producing large numbers of NCD publications in leading journals with scientists from developing countries, and have been successful in establishing sustainable programs.

Building the Supercourse network

Our goal is to expand our existing NCD network to create Supercourse programs in leading national universities in OIC countries. We will establish NCD epidemiology research programs and start network building. NCD training must be interdisciplinary, so we will target national universities. We have already been collaborating with 600 universities in OIC countries and have in place a large network of researchers in OIC countries. Universities are likely to reach out to a Supercourse program as more and more universities are seeing the benefits of international components. Students will take an additional 15 hours of courses, and pay additional tuition, and some of the money raised will flow to the faculty. The incentive for the faculty is global prestige, plus of course the money they will receive for teaching the course.

Supercourse training

We have already started to build the curricula needed for NCD Supercourse Training. The Supercourse (www.pitt.edu/~super1) is described in depth in a progress report. Briefly, it consists of a network of 56,000 primarily academic faculty from 172 countries. We have a research network of 8,006 faculty from 39 low-income countries (see Table 1) and 1,257 individuals from 42 middle-income countries. Most of these are from academia. Overall, there are more than 9,000 research faculties from

Table 1 Faculties from Low-Income Countries Participating in Supercourse.

Afghanistan	12	Niger	6
Bangladesh	32	Nigeria	160
Burkina Faso	6	Pakistan	624
Cambodia	7	Papua New Guinea	8
Congo	8	Senegal	14
Eritrea	4	Sierra Leone	2
Ethiopia	16	Solomon Islands	2
Gambia	6	Somalia	8
Ghana	19	South Korea	49
Haiti	4	Sudan	58
India	6700	Tajikistan	6
Kenya	37	Tanzania	20
Lao PDR	2	Togo	2
Madagascar	1	Uganda	44
Malawi	10	Uzbekistan	17
Mai	14	Vietnam	21
Mangolia	6	Yemen	8
Mozambique	8	Zambia	10
Myanmar	9	Zimbabwe	21
Nepal	25	Total	8006

81 countries. These figures show that after establishing the Supercourse in OIC countries we can expand to build capacity in other low- and middle-income countries, as we already have the human network in place along with State Department, WHO and UN backing.

There are 26 low- and middle-income Islamic countries where we have potential participating faculty. These include Afghanistan (12), Albania (4), Algeria (2), Azerbaijan (2), Bangladesh (32), Burkina Faso (6), Cameroon (28), Cote D'Ivoire (2), Egypt (190), Gambia (6), Guyana (4), Indonesia (92), Iran (116), Iraq (6), Jordan (6), Mali (14), Morocco (12), Mozambique (8), Nigeria (180), Pakistan (624), Senegal (14), Sierra Leone (2), Somalia (8), Sudan (58), Tunisia (4), Turkey (29), Turkmenistan (6), Uganda (2) and Yemen (4). Including OIC countries, we have 1,531 faculties from 30 countries already participating with us.

The goal of the Supercourse is to increase the number of individuals throughout the world who are trained in disease research and prevention. Currently there are 3,455 lectures represented. Our scientific team include many leading experts in NCDs such as Lewis Kuller, Henry Blackburn, Richard Doll, Peter Bennett and Baruch Blumberg. We also have 14 lectures from 50 Nobel Prize winners, the former US Surgeon General, the former heads of the CDC and NIH. The lectures are up-to-date and original, and students and educators across the world tell us that they are of outstanding quality. So we are already the major supplier of high-quality NCD training materials in the world.

Furthermore, we have an effective system for disseminating our lectures, with 42 mirror servers, 15 of which are in developing countries. The Supercourse websites receive between 80 million to 100 million hits a year. Last year we taught more than 1 million students about disease prevention (estimated from web usage statistics), probably more than any other program.

From slides to curricula

We plan to take several approaches to build a flexible shared curriculum. We have already mastered the art of shared curricula and have collected the building blocks of curricula: slides and lectures. Curricula are composed of courses, courses are composed of lectures, and lectures are composed of slides. By rearranging lectures we can create different courses and curricula. We want to improve the education of as many of our future scientists as possible and help them interact and learn from the multiple facets of NCD prevention. We will do this by establishing a system of slides and lectures that can be rearranged by teachers to establish different curricula. We provide the raw materials, but it is the university instructor who converts the lectures into courses and curricula. This is a very flexible system. Slides and lectures are the 'seeds' of interdisciplinary courses and curricula and make it much easier for local instructors to teach in other areas. We have also found that teaching students from many countries means that the lectures have to be translated, and Supercourse does this.

The Supercourse curriculum already comprises 221 epidemiology lectures, 157 from developed countries and 64 from developing countries. In the past 12 months, 66,300 individuals have seen these lectures. As developing countries make up about 20% of this usage, at least 13,000 individuals in low- and middle-income countries will have seen them (the number is likely to be higher as we have not included usage at the 42 mirror servers). The average score of our lectures overall is 4.2 out of 5, from 10,000 reviews.

To help build curricula that cover a variety of aspects of NCD, we have 40 lectures (31 from developed and 9 from developing countries) on cancer, 73 (51 developed and 22 developed) on cardiovascular disease, two on lung disease and three on obesity. We have numerous lectures describing research methods in chronic diseases and 30 lectures on generics. There are many different lectures examining the aetiology, prevention and implementation science of NCDs, so all the major focus areas of research training are covered.

One of the best gauges of web impact is Google's page ranking. A Google search of the keywords 'non-communicable disease lectures' at the time of writing ranks our Supercourse lectures in the top position. If we search on 'prevention lectures' there are 6,600,000 sites listed, and again we are ranked first. We are the top-rated site for epidemiology lectures out of 700,000. For 'global health lectures' on Yahoo we are listed as first of 27 million. We are the highest-rated lecture site for NCDs.

The existing network and Supercourse lectures means we have already built a large, robust global faculty network engaged in NCDs, and many more students are already being taught about NCDs as a result.

Distribution of lectures to universities

We use many different approaches to distributing our lectures. They are not copyrighted, so we encourage people to share their lectures with their friends. In addition to our Supercourse site in Pittsburgh, Pennsylvania, we have 42 mirror servers at universities in Nepal, Egypt, Sudan, Thailand, China, Mongolia, Mexico, China and Egypt, among others. A mirror server aids distribution because someone in Nepal finds it much faster to

access a lecture from a server in Nepal than they would if the server is in Pittsburgh. Also, having the Supercourse at your local university in Sudan produces pride of ownership.

Our Chinese network of 700 medical students is currently translating the lectures into Chinese. The educators at universities in low-income countries become the distributors of the lectures through their teaching. We share the best materials with the teachers, who can then present them to their students through DVDs, rather than over the Internet. To this end we have created more than 12,000 DVDs contain 3,400 lectures. We do not just give the DVDs away, however; rather, we request that the DVDs are gifts meant to be given away, and we ask people to make at least five copies for their students and library. In addition, a governor in a state in Nigeria with a large Muslim population has made 1,000 copies and distributed the lectures to every college and university in Nigeria. At least 1 million students each year are learning from our lectures, and 20% of these are from low- and middle-income countries. We plan to build further mirror servers in all of the OIC countries. If funded, we want share our content as widely as possible.

Mentoring

The Supercourse Training will target experienced faculty in OIC countries, many of whom are not engaged in NCD research. In this way, we will develop a virtual mentoring system, pairing senior faculty from developed countries with the Supercourse Training students interested in their areas. So, for example, a student in Jordan interested in diabetes research can ask questions directly to Peter Bennett, a world leader in diabetes research.

We will establish five courses, have them translated into Arabic, and build an expert knowledge mentoring network. Our educational model represents medium- and long-term training. In general it will take about a year to complete the five courses in addition to the students' graduate course work. As part of this, there will be a research internship on one of the Supercourse projects. Student and expert mentoring will be available in school, but also after graduation, so the mentor network could represent life-long learning.

Sustainability

One of the critical questions facing projects such as Supercourse is this: 'What will happen when the money runs out?' Many projects just end when grants do because it takes money to support research. During the past five years, we have received no funding from the NIH, yet our research has expanded to become one of the largest global health projects in the world. This is because we have developed a spirit of volunteerism where anyone can contribute, and this makes our efforts extremely inexpensive. The building of NCD registries is relatively cheap, and we have developed an effective training program for 'shoe leather' epidemiology.

We have been successful in helping countries 'jump-start' their research efforts, not by giving them money, but by sharing our knowledge and mentorship. We have worked with countries to help them publish their results in leading journals. In addition, as highlighted by our WHO project, which received no funding, the research can be easily initiated and sustained through the efforts of volunteers once the infrastructure has been established, although that does need initial funding. After five years, the centers will be self-sufficient in research. We will need funding to establish the certificate programs and monitoring systems. To achieve this we are forming alliances with the US State Department, the WHO and the OIC countries themselves. We expect that the individual universities will pick up these programs, and that the WHO and the State Department will help.

Short-term training and Long-term mentoring

Our Supercourse model is a 15-hours certified course with long-term local and global mentoring. This has has proven to be a very successful model to build capacity in other areas. The Field Epidemiology Training Program (FETP), for example, is a CDC training program designed to develop epidemiologic expertise among health professionals, modelled on the CDC's own Epidemic Intelligence Service (EIS). The program is available in 34 countries, including Saudi Arabia, Egypt, Jordan and Malaysia. As with the Supercourse, FETP trainees and fellows should have

core competencies on the following knowledge domains: epidemiology, biostatistics, communications, information technology, leadership and management. Trainees do a lot of practical work and 'learn by doing'. In many ways these are the original 'implementation scientists'. The FETP program has been highly successful in building an epidemiologic science infrastructure in developing countries. The Supercourse has the same core, with a short-term certificated course followed by long-term mentoring. We will also target field surveys, environmental outbreak investigations, perform disease control and prevention measures, and establish chronic disease surveillance systems, but only in the area of NCDs. Like the FETP, the Supercourse has the Internet at the heart of its global mentoring and collaboration. Indeed, Supercourse currently has more than 1,000 CDC collaborators.

The International Diabetes Federation, the University of Cambridge and the WHO have been running 10-day training courses in diabetes epidemiology since 1981. We have been faculty in most of these courses. We wanted to see what impact the Cambridge courses have had on creating diabetes epidemiologists. We took the list of names from the third (1987) and fourth (2000) courses and identified all the students who were from developing countries; there were 19. We then tracked their publications using Google Scholar and Pub Med. The results were striking. During that 20-year period these students from developing countries produced 349 publications, with a median of 9. They were nearly all in excellent journals. Many of the students from developing countries collaborated with the faculty and other students from outside their countries and have continued to keep in touch. Clearly the Cambridge course had an enormous impact.

When the short courses began in 1981 there were only about five diabetes epidemiologists; now there are over 600. Virtually all the publications about diabetes epidemiology from developing countries were from researchers or their students who were trained on the courses. The diabetes short courses were modelled on the American Heart Association's cardiovascular courses, which were just as successful. There are several similar university courses, such as the University of Minnesota's short course on epidemiology, which takes a similar amount of time as our proposed course. The Minnesota course has been given for 40 years, with the students receiving certificates.

The graduates from these programs have become leaders in their field. Short training courses coupled with networking and mentorship have a successful history of producing researchers in low- and middle-income countries. We will engage the developers of these programs for our own course.

Conclusions

We already have a huge NCD network, outstanding content, and have produced an enormous increase in teaching about prevention research and education in low-income countries and elsewhere. In addition, we are probably one of largest US collaborators with Islamic nations. Together, we can make a huge difference to the teaching of NCDs in developing nations, and so help to raise the level of their research in these areas.

12

Smart IP Protection can Bridge the Technology Divide

Prabuddha Ganguli

With respect to technology, the gap between the 'haves' and the 'have-nots' has increased to the point where it seems unbridgeable. The more technology advances, the wider that gap becomes.

Those who develop technologies are naturally keen to protect their rights using the diverse tools of intellectual property rights (IPR). This leaves the technological have-nots in a quandary. Should they venture themselves into the technology development process? Or should they explore ways of acquiring the technologies from those who developed it?

Perhaps, with a bit of cooperation from both sides, the tools of IPR can be used to effectively bridge the technology divide. Here I will explore some of the ways in which national IPR policies can work within competition law with a view to protecting national developmental needs, leading to steady capacity building and the balanced sharing of benefits. To illustrate how this can work in practice, I will consider technologies from a variety of fields.

The Politics of knowledge

The mainstream system of IPR works quite well in the developed world, where it was developed, but it is being progressively drawn into the developing world, where the evolution and application of technologies

are still in their formative stages. The interface is unsatisfactory, creating barriers that translate into issues of non-acceptance and emotive debates. We need to understand the reasons for these barriers and find ways of either reducing the threshold of non-acceptance or overcoming them as we move towards our goal of sustainable development.

The innovation process is driven by excellence and leads to competition, resulting in development and growth. This is all dependent on a variety of factors such as knowledge, creativity, vision and action. However, the tools of IPR divide knowledge into proprietary and non-proprietary domains—this is the basis of what I call 'knowlitics', the politics of knowledge, which has taken center stage among the emerging socio-political knowledge-trading platforms for dealing with 'owned knowledge'. The key question is how we exploit the proprietary and non-proprietary domains of knowledge for social benefit. It is in this context that national policies on innovation and IPR can play a key role, and the concepts of 'knowledge prospecting' and 'knowledge piracy' become important. How can we transact owned knowledge to make it mutually beneficial to those who created it and those who receive the owned knowledge?

The global technology scenario has undergone a structural and operational shift during the past couple of decades, driven by demands for faster business-led innovation in the marketplace. The phases of technology generation, application and trading have now come together as companies strive to survive the fierce competition and maintain their competitive advantage. This has forced research and development, which traditionally operated in two distinct phases of 'upstream' and 'downstream' research for academic and commercial institutions, respectively, to merge into a 'midstream' mode. This is now heading towards what I describe as a 'turbulence' and 'rapids' mode, driving industry ever closer to the academic world to make the best use of 'intra-institutional' and 'extra-institutional' knowledge for delivery to the marketplace.

Bridging the divide

Issues related to the ownership of knowledge are becoming linked with the expectation of fair benefit-sharing arrangements between partners.

Managing IPR at every stage of the innovation chain demands new value systems and skills, and these are the key issues to be resolved if we are to bridge the great divide. Can collaboration be achieved between unequal partners—between the haves and the have-nots? I believe that collaboration is indeed possible, and that IPR can act as the bridge when both sides play the game fairly.

At this stage it would be helpful to visit the 'innovation value chain' and explore its connectivity with the management of IPR. At the concept stage, the ratio of the realizable value of intellectual property (RVIP) to its potential value (PVIP) is low. However, as we move along the innovation value chain, the RVIP/PVIP ratio increases and the risks become lower, as science is progressively transformed into technology and its value to business increases. It is important to note that IPR needs to be managed throughout the innovation chain, from the idea stage to the marketplace and beyond as businesses seek to gain and maintain their market advantage.

One way of progressing down the innovation chain is to partner with bodies with the funds, facilities and means to transform the concept into a working reality in the marketplace, with benefit-sharing proportional to the value of the IPR in the entire value chain. We should therefore try and move away from thinking of technology development and transfer as a 'post-science and technology activity' but one that occurs alongside it. Developing countries do not lack good ideas, but they may lack the infrastructure, funds and means to transform them into market realities. However, judicious collaborative activities across the technology divide between developed and developing countries, with proper management of IPR at every stage, could resolve several of the issues arising from knowlitics. Those in the developing world need to develop their skills to manage the intricacies and complexities of innovation and IPR. With the development of comprehensive national policies on innovation and IPR, developing countries should be able to promote the generation of ideas, put the ideas into practice, bring them to a concept demonstration or a feasibility stage, protect them using the appropriate tools of IPR, and then strike global partnerships with fair benefit-sharing arrangements. Only then can such partnerships help to bridge the divide.

Making partnerships work

The Indian government has created a variety of platforms to promote innovation, develop technologies and bring about the technology transfer needed for commercialization. Rajagopala Chidambaram, the Principal Scientific Adviser to the Indian Government, has been promoting a comprehensive concept in which basic research and directed basic research are supported for national projects, some of which could have only a social mission whereas others could be directed towards problems that are significant to industry. Another possibility is a model for public-private partnership in an industry-academic consortium, at least in the pre-competitive phase, after which industry could take the fruits of the partnership to the marketplace. Such a model needs to be well structured, especially in terms of the ownership of IPR at various phases of the project. Well-crafted national policies on innovation would be needed to make such a model operative.

There are many ways of promoting small–sized and medium-sized businesses. One option is to create business clusters, where various IPR tools are used to enhance brand image, taking advantage of collective bargaining to procure competitive technologies, and collectively managing IPR in the cluster to make the best use of the available resources. Similarly, innovation policy could support projects of national importance, so that the various institutions participating in the networked research pool their IPR to create strategic, national IPR portfolios. These can then become a rich national resource for initiating international networks to develop partnerships in various parts of the innovation value chain, thereby bridging the technology divide and promoting the transfer of technology.

Success stories

Developing nations have had some success in their efforts to bridge the technology divide. India, for example, has made significant changes in its economic and science and technology policies over the past six decades. Consistent investment in technical education has strengthened the nation's human resources and infrastructure, and a series of progressive fiscal and industrial policies have also supported India's position with respect to

science and technology. There has been a rapid influx of wholly owned companies and subsidiaries of international corporations that have set up R&D centres in India. The outsourcing of services, including contract manufacturing, contract R&D and international science and technology programs, to India are a clear sign of international confidence in India's strength in these areas. India now has more plants outsourced by the United States for the manufacture of drugs than any country.

Similar successes in South Korea, Taiwan, China, Cuba and Brazil show that the developed world is increasingly starting to rely on the science and technology expertise of emerging economies. The gap is already starting to close.

The Way Ahead

Several important problems remain to be overcome, however. Innovation in developing countries is still sometimes stifled by the lack of available funding, leaving innovators unable to make progress with their IPR globally, resulting in lost opportunities and revenue. Sometimes they are unable to derive the full value of their IPR owing to fragmented innovations, a lack of information about IPR, and inadequate skills in managing IPR and conducting strategic negotiations. Another problem is the high cost of litigation, which prevents the owners of intellectual property in developing countries from initiating the necessary steps to enforce their IPR and prevent biopiracy, for example.

National IPR policy is the key to overcoming these challenges. For example, a strategy must be developed to ensure that the very process of IPR does not itself become a barrier to innovation by impinging on the right of researchers to experiment with patented inventions in their own countries. Researchers need to be given the freedom to innovate. Policies must be developed to create the human resources and infrastructure needed to help innovators manage their IPR throughout the process of technology development, and to help them take commercial advantage of their innovations in the marketplace. Only when developing countries have successfully provided the support their science and technology sectors need can they hope to close the technology divide.

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A New era for Scientific Institutions

Mohamed Raouf Hamed

Change is constant; it is always happening, and how we deal with it plays a large role in how successful we are. That applies just as much to organizations as it does to individuals. Here I will explore how change affects scientific institutions. I will try to delineate the dynamics that bring about positive change, and to show the requirements needed for these dynamics to be optimized and sustained.

Three major factors must be considered. The first factor relates to the challenges produced by the processes that lead to globalization. An example here is the system of intellectual property rights, which affects changes in world trade, whether they originate from multilateral agreements (through the World Trade Organization) or bilateral ones (free trade agreements).

Another type of challenge is the spiral of negative outcomes of the globalization processes, such as the international financial crisis. The second factor relates to developments in knowledge and knowledge management. Finally, we must consider the managerial requirements of institutions in developing countries, including small- and medium-sized enterprises as well as research organizations, such as universities, research centers or research and development departments in companies.

Developmental gaps

Institutions should have two major targets: to optimize their performance, and to ensure that they take full advantage of growth opportunities. These

targets can be viewed as gaps in the development of an institution; how well institutions fill these gaps is critical to their success.

The relative importance of these gaps may vary between organizations, depending on their size, type of business, health and direction of thinking at the senior management level. But both gaps must be considered if the organization is to make progress. Indeed, achievements relating to each gap affect (and are affected by) the institution's success in dealing with the other one. Furthermore, achievements concerning each of the two gaps, as well as the areas in between the two gaps, affect both the genesis and the continuity of the enterprise's innovative machinery.

But before we can discuss how all these activities affect innovation, we need to identify the elements of each gap.

The performance gap includes routine activities in areas such as production, quality control, marketing, planning inventory and training. In contrast, the opportunity gap includes activities such as intelligence work (collecting information and predicting possible future changes and challenges), preparing to face challenges and making changes, which may represent progression for the institution and may present fresh challenges.

Filling the performance gap requires information about the functioning of the organization. This may be gleaned routinely throughout the ongoing work of the organization or obtained at periodical re-evaluation breaks, where the work is put on hold so that all employees have an opportunity to provide input and exchange in the free exchange of views. Additionally, accidents, mistakes and unusual challenges that arise can be a particularly rich source of information about how the organization is performing.

It is understandable that information about the performance gap will have two main consequences. The first consequence is the direct improvement in the performance behaviour of one or more of the elements of the gap. The second is the possible rise of situations that require treatment by improving performance. This means that activity at the performance gap level can help providing issues that have to be considered by the opportunity gap activity. Through both possible consequences, the input comes at the innovation level.

Planned efforts designed to cross or fill the opportunity gap (intelligence, prediction and systemic actions) will result in acts such as modifying (or strengthening) the subsystems that deal with the performance gap, generating new subsystems, defining new targets for research and development, or linking with others through such mechanisms as outsourcing and forming alliances. Again, the consequences of activities relating to the opportunity gap also affect both the performance gap and the efficacy of the innovation machinery.

Relationship with the innovation process

The relationship between the two types of gaps and the innovation process is shown in Figure 1. As the figure shows, activities grown within each of the two gaps affect the activity in the other one. Moreover, work on each gap results in developmental actions that consequently lead to innovation. It can be seen that the pathway to innovation may require the performance of research. The innovation will also lead to a further increase in the demands of the two types of gaps.

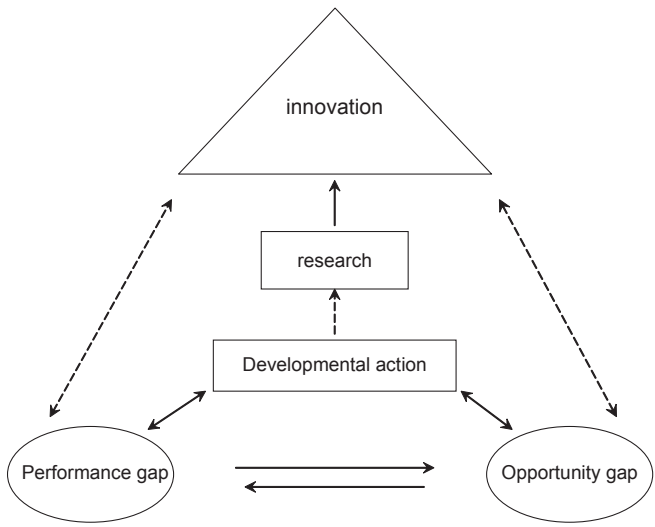

Figure 1 The relationships between the performance gap, the opportunity gap and innovation.

In taking these steps to reach developmental or innovative change, two further factors should be deeply considered: the procedure for crossing the gaps, and the nature of the organizational relations.

Phases of developmental work

Procedures may be classified into three major types: exploration, planning and transformation into action. In exploration, the major target is the collection of pertinent information, whether it relates to internal or external systems. This information must include relevant circumstances and organizations at local, national and international levels. After gathering this information, there needs to be a creative planning stage in which the information is analysed and used imaginatively to create a new intellectual view and to map out possible scenarios, but this requires a realistic understanding of the constraints. When this work has been completed, the plan can be put into action. This requires different objectives to be allocated to different parts of the organization.

The crucial factor that controls whether these three procedures, or phases of activity, are successful is the nature of the relations between the different parts of the organization through which they were conducted.

Three questions can tell us whether the change will be successful at the operational, functional and strategic levels. First, was the change induced and implemented collectively by all of the necessary organizational subsystems and their manpower? Second, will the targets and consequences of the change benefit all the subsystems in the organization, or just those selected?

If the answer to the first question is 'yes', then the change is based on societal creativity. It is accordingly expected to affect the innovative machinery of the organization in a highly positive way. If the answer is 'no' then the organization lacks the drive of societal creativity. As a consequence, the potential for filling the gaps and creating or maintaining the innovative machinery is limited. The answer to the second question can easily be predicted, as it will be correlated with the answer to the first question. If the answer to the first question is 'yes', indicating the organizational dependence on societal creativity, then it is likely that the

whole organization will benefit from the change. A 'no' to the first question predicts a 'no' for the second question too.

People are the cells of societal creativity

The two questions mentioned above are not purely idealistic. Globalization has led to some highly negative outcomes, such as waves of deployment and the current international financial crisis. Such negative outcomes are clearly associated with the marginalization of ordinary people by globalization. In other words, the interests of ordinary people were neglected to maximize the performance and opportunity gaps during globalization. The possibility of empowering societal creativity was displaced by unnecessary and harmful conflicts across the world.

In our opinion, both the successful crossing of the performance and opportunity gaps, and the optimization of the exploration, planning and transformation phases, are dependent on empowering ordinary people. This consideration stems from the most important outcomes of basic concepts in the areas of knowledge management and digital economy.

The most basic unit in any organization is the individual person. If this individual is empowered by learning and activation then his or her potential is physically and mentally networked and integrated with others who are similarly treated. This group of individuals is then transformed into a team. The processes that led to this transformation from the individual status into a team status are empowerment, activation, networking and integration.

These processes can also be applied to each team. The empowered, activated, networked and integrated teams will then result in an empowered organization, in which two parallel positive outcomes are addressing the potential for continuous positive change. These are: continuous redesigning of the internal organizational processes, and continuous developments in the external organizational linkages.

The optimization of the organizational redesigning and linkaging processes ensures the effective crossing of the performance and opportunity gaps; it is a direct consequence of the highly successful explorative, planning and transformation activities.

The positive reaction among the individuals and teams (outlined in Figure 2) can induce the basis for societal creativity (Hamed, 2004), the creation of something that was not previously present. Such creativity can be regarded as an optimal outcome from the socialization reactions discussed by Nonaka (1994).

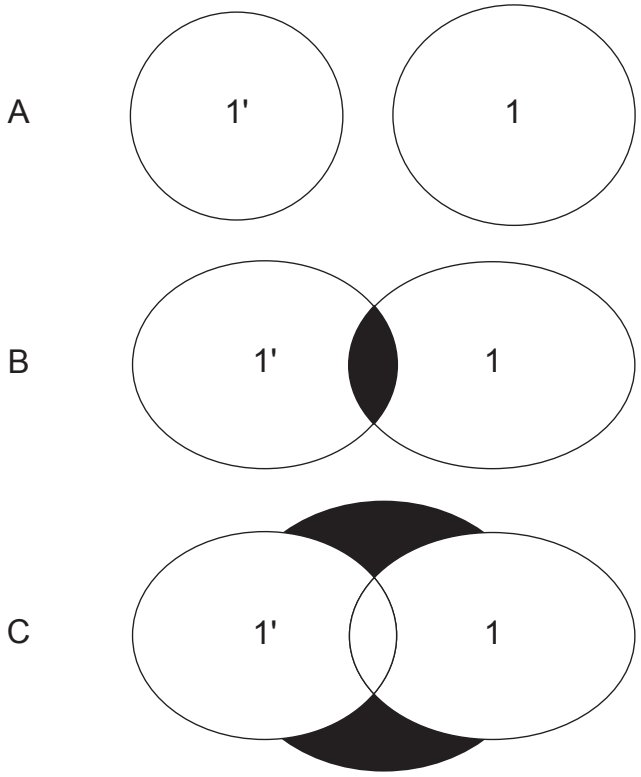

Figure 2 Societal creativity. In the top section, if 1 and 1' represent different entities (individuals or teams) that do not interact, their presence close to each other will not be productive. In the middle section, the two entities overlap, but that is the only thing that happens. In the bottom section, however, the two entities react with each other in a positive way that helped them produce sets of characters or capabilities that did not previously existing in either of them. Their collective reaction helped them to create. This is the basis of societal creativity.

Conclusions

The induction of positive change, which stimulates the innovative machinery of small-sized and medium-sized enterprises and research institutions, is dependent on the methodology used. The optimal activation of the capabilities of the individuals within teams in the organization, and the optimization of the capabilities of the teams themselves, are reliable bases for successfully crossing the performance and opportunity gaps.

The steps for crossing these gaps can be approached systematically through exploration, planning and transformation activities. When empowered individuals and teams carry out these activities, the organizational dynamics can be maximized and the organization can reach its full potential.

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3

GREEN SHOOTS IN FOOD AND AGRICULTURE

14

High-Energy Foods to Tackle Childhood Malnutrition

Stephen W. Jarrett

The United Nations set up the Millennium Development Goals to eradicate extreme poverty and hunger and to reduce childhood mortality by the year 2015. More specifically, they were designed to halve the prevalence of under-weight children between 1990 and 2015, and to cut the under-five mortality rate by two-thirds during the same period. Nutrition is a desperately neglected aspect of maternal, newborn and child health (Horton, 2008). Globally, the main risk factors for children less than five years old are stunting, severe wasting and intrauterine growth restriction (Black et al., 2008). An estimated 19 million children under five years of age suffer from one of the severest forms of malnutrition, severe acute malnutrition, which is defined as being more than three standard deviations below the median weight for the height of the reference population (Bhutta et al., 2008). Of these, an estimated 5 million live in sub-Saharan Africa, so tackling malnutrition there is essential if the Millennium Development Goals are to be achieved.

Traditionally, children with severe acute malnutrition have been hospitalized and treated with a milk-based powder mixed with boiled water, known as the F100 therapeutic diet. But very few cases of severe acute malnutrition are treated, limited by the capacity of in-patient care and treatment plus the difficulties facing parents or families in bringing their child to a feeding center and staying there for at least a month.

Mothers have a high workload and often cannot afford to spend four weeks away from the fields and their other children to stay with a severely malnourished child in a feeding center (Walker, 2004).

Ready-to-use therapeutic food

Development

In the late 1990s, a French scientist, André Briend, along with a French company, Nutriset, developed a nutritional paste that is equivalent to the F100 therapeutic diet but requires no further preparation (Briend et al., 1999). This ready-to-use therapeutic food (RUTF) is classified as a high-energy, fortified, ready-to-eat food suitable for treating children with severe acute malnutrition. The great advantage is that treatment with RUTF can be given at home, once the child has been diagnosed by a health worker as suffering from severe acute malnutrition and there are no medical complications that would require medical supervision (about 15% have medical complications). Community-based management of severe acute malnutrition had a 76.8% recovery rate and a fatality rate of only 4.7% when given to 7,400 children with severe acute malnutrition in programs in Malawi, Ethiopia and Sudan (Collins, 2004). In contrast, fatality rates in hospitals for children with severe acute malnutrition in developing countries average 20–30%, and this has remained unchanged since the 1950s (Collins et al., 2006).

In 2007, a joint statement by the World Health Organization (WHO), the United Nations World Food Programme (WFP), the United Nations Standing Committee on Nutrition (SCN) and the United Nations Children's Fund (UNICEF) endorsed the community-based management of severe acute malnutrition with RUTF. This endorsement paved the way for more countries to adopt RUTF and for an expansion of programs to tackle this severe form of wasting in children. To date, at least 25 countries have adopted this approach, establishing policies and protocols to guide health and nutrition workers in expanding the treatment of children with severe acute malnutrition.

RUTF, as originally formulated, is an enriched peanut (groundnut) paste. Its ingredients include peanut paste, milk powder, vegetable oil, sugar

and a mixture of vitamins and minerals. An emulsifier is normally added to stop the peanut oil separating. As RUTF is not water-based, bacteria cannot grow in it, and it can be safely used at home without refrigeration and even in unhygienic situations. This food is not suitable though for children under six months old, however.

The production of RUTF is relatively simple. Peanut paste must be produced or bought, with the assurance that it has been properly prepared and the peanuts have been tested for aflatoxins (Williams et al., 2004). The ingredients are weighed to the correct amount according to the batch size, mixed together and subjected to a first grinding. They are then blended continuously until a homogenized paste is developed, usually within an hour, depending on the blending machine used. The paste is then packaged, either by hand (in bottles) or in a semi-automated (in sealed yoghurt cups) or fully automated (sachets) fashion, depending on the type of machinery available and the shelf life required. Packaging capacity is the bottleneck, so this is what dictates the production capacity, if the ingredients are available.

Production in Africa

Nutriset, which developed the product, has already nurtured the development of local franchises in Africa, and RUTF production facilities are functioning in Ethiopia, Malawi and Niger. It has also licensed Valid Nutrition, a charity based in Ireland, to establish production facilities in Ethiopia, Kenya, Malawi and Zambia. The original Nutriset product, branded as Plumpy'nut, is patented in 30 African countries, but not in some countries with large populations, such as the Democratic Republic of Congo, Ethiopia, Nigeria and South Africa. RUTF can be safely and easily produced in small or large quantities in most settings worldwide (Manary, 2006). Generally speaking, however, quality can be better assured and maintained when it is produced at a commercial scale.

RUTF is a medical treatment, made specifically to treat severe acute malnutrition, so it requires a prescription from a qualified health worker. As such, it cannot be offered for sale on the retail market. Other ready-to-use formulations exist that can be produced in the same way and directed towards the supplementary or complementary feeding of children where there is insufficient food with the nutrients required for infants and children

under three years. These other formulations can be marketed openly, and they would benefit from having the same quality controls as those used in RUTF production.

There are indications from Ghana that mothers are willing to pay a small amount to acquire ready-to-use complementary food to enhance the diet of their young children (Adu-Afarwuah et al., 2007). Initial trials are underway using ready-to-use foods to supplement the diets of HIV-infected children and adults, as HIV infection increases the energy and nutrient requirements, and nutritional deficiencies increase the progression of HIV infection (Friis et al., 2008). Ensuring that HIV-infected children and adults have proper nutrition, as a complement to antiretroviral medicines, is an essential component of the response to HIV/AIDS in sub-Saharan Africa and elsewhere (Anabwani and Navario, 2005). The incentive for local producers to start producing RUTF, therefore, may be the long-term market demand for a range of ready-to-use foods for different population groups.

There are specific advantages to producing RUTF in African countries. National production enhances local capacity and distribution. Local ingredients are used wherever possible, such as peanuts, vegetable oil and sugar, although milk powder and the mixture of vitamins and minerals may need to be imported. National production also improves product recognition and acceptability, and local languages can be used on packaging and inserts. In addition, national production attracts political support, which in turn can help focus attention on the malnutrition problems the country is facing.

Production is organized along production lines with a specific capacity. The smallest capacity thought to be commercially viable is the production of about 1.4 tonnes per day, achieved with a 200 kg blender and a turnaround time of one hour for mixing and blending ingredients, with seven rounds per shift. If there are 250 production days per year, this equates to an annual production capacity of 350 tonnes. At a price of US$4,000–4,500 per tonne, this translates to US$1.4–1.6 million annually. Adding a second shift can double the value, with each shift requiring 5–6 trained workers to complete the production process.

Assuming that a child with severe acute malnutrition requires 10–15 kg of RUTF over a period of six to eight weeks, and that Africa has 5 million

children with severe acute malnutrition, the continent would need between 50,000 and 75,000 tonnes of RUTF every year. This is a conservative estimate, however, as the number of children is based on prevalence figures and the actual incidence may be much higher. In addition, HIV-infected children with severe acute malnutrition require twice as much RUTF. In reviewing Africa's need for RUTF, UNICEF consulted its development partners and decided that a reasonable first production target for Africa should be 50,000 tonnes by the end of 2011. For comparison, global RUTF capacity, including production in Europe and Africa, was between 16,000 and 18,000 tonnes at the beginning of 2008. A tripling of capacity over three years is being sought.

Interest in local production in Africa is increasing, with new franchises being established or planned in Ghana, Mozambique and Tanzania. In addition, production in the Democratic Republic of Congo, which halted in 2007 over difficulties in accessing ingredients, needs to restart. New companies are also poised to enter the market, and initial discussions on franchises or joint ventures are taking place in Madagascar, Nigeria, Senegal and Sudan. Production in South Africa was set to begin in 2008.

The cost of production varies according to the production capacity, the machinery used, the cost of ingredients and labour costs. A rough initial estimate, based on experience in setting up franchises in Africa with a capacity of 350 tonnes, is that around US$1.2 million in start-up investment is required for the first year of operation. This is needed to buy and install machinery and quality-control instruments, train staff, pay for labour and utilities, and contract for the first 350 tonnes of ingredients, with around 65% of the money needed for the ingredients. Establishing a capacity of around 25,000 tonnes in Africa, assuming that about half the demand is met from within the continent, would require start-up costs of around US$80 million.

These figures are merely a rough guide, as the model that is emerging is a mix of large, medium and small production facilities in both developed and developing countries. Africa has a mix of country and regional facilities in 15–18 countries.

Benefits

The specific objectives of producing RUTF in Africa are:

- To scale up the availability of RUTF to treat severe acute malnutrition in children
- To establish effective and commercially viable national production of RUTF, based on affordability and sustainability
- To ensure sustainable supply by adopting in each country a balanced sourcing of RUTF between national and regional producers in developing countries and producers in developed countries, to cope with production spikes during emergencies and for any failure in national production
- To improve the economic returns of farmers growing the ingredients, recognizing that women are the principal growers of peanuts and livestock managers, and to increase employment opportunities with national production

The alliance of a broad set of partners is central to the successful treatment of children with severe acute malnutrition, including the sustained supply of affordable RUTF. Experience in community-based management was initiated through the activities of non-governmental organizations (NGOs), which will continue to treat children and explore new methods of treatment. With governments adopting this strategy, scaling up the use of RUTF will largely be the responsibility of the public-health services, through their primary care personnel acting in peripheral health facilities with outreach into the communities. International agencies, such as WHO, WFP and UNICEF, together with donor governments, will continue to provide part of the funding base, given that severe acute malnutrition is most prevalent in countries that have extremely limited resources.

Academic institutions will continue to learn from the experience of introducing community-based treatment, in developing new formulations based on locally available ingredients, and in tracking the effectiveness and the costs and benefits of specific actions taken. Ultimately, it will be the private sector that scales up production, based on projections of demand from governments and NGOs. Producers in both developed and developing countries will be engaged in production, often in partner arrangements. Private individual investors have emerged as the main source of investment in production in Africa, although donor governments have given this their support.

Challenges

The national production of RUTF in Africa is a promising case of research being translated into local solutions to treat children with severe acute malnutrition, a significant underlying cause of child mortality. But challenges remain, although some have potential biotechnological solutions. Peanuts are a core ingredient of RUTF, but in sub-Saharan Africa most peanuts are grown by smallholder farmers under drought conditions. If some of the drought-tolerance traits found in crops such as sorghum or millet could be incorporated into peanuts, productivity would increase, and losses from cyclical drought would be reduced (Paarlberg, 2008). Removing aflatoxins from the peanut crop is another challenge, as the toxic effects of aflatoxins on immunity and nutrition cause health problems (Gong et al., 2004). The use of biopesticides that apply benign spores in soils around crops is a new area of research that could produce significant results for crops affected by aflatoxins, including peanuts.

Another core ingredient is milk, as at least half of the proteins contained in RUTF should come from milk products. But milk production in Africa is very low, at around 26 litres per person per year, according to the UN Food and Agriculture Organization. Like peanuts, milk is mainly produced on smallholdings run by women. Genetic improvements in cattle herds are considered a critical factor for increasing milk production in Africa (Alary et al., 2007).

Conclusions

RUTF production in Africa is already emerging as a success, but additional biotechnological research can further enhance the productivity of key ingredients. With RUTF production set to increase over the next few years, Africa is taking steps to reduce childhood mortality, one of the key Millennium Development Goals. The multiplier effect in enhancing the economic situation of smallholder farmers, who are principally women, can produce additional benefits in the drive to meet some of the others.

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15

Strategies for Biofortification in Brazil

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In Brazil, the intake of vitamin A and minerals such as iron and zinc is below the recommended levels and their bioavailability in the diet is low. Biochemical studies show that some groups of the population have so low levels of micronutrient that intervention is needed. Most attempts to combat micronutrient deficiency elsewhere in the developing world have focused on providing vitamin and mineral supplements to the poor and on fortifying foods with these nutrients during processing after they have been harvested. But are these the best strategies?

In Brazil, the focus is instead on biofortification, an intervention strategy that is being developed to increase the content of particular micronutrients in staple food crops by agricultural, agronomic or biotechnological means. This means that the micronutrients are already in the crops when they are harvested, so they do not need to be added afterwards. When consumed regularly, biofortified foods will lead to increased micronutrient intake. Biofortification can complement the existing strategies and provide a sustainable, low-cost way of combating malnutrition.

Brazil has two biofortification programs: the HarvestPlus Challenge Program on Biofortification and the AgroSalud Program, both coordinated by the Brazilian Agricultural Research Corporation (Embrapa). The difference between the two programs is that the HarvestPlus Challenge Program focuses on breeding micronutrient-rich plant varieties, whereas the AgroSalud Program focuses on Latin America and the Caribbean and on post-harvest processing. The main food staples being studied in Brazil are cassava, sweet potato, rice, common beans, maize, wheat and cowpea.

Micronutrient deficiencies in the developing world

It is estimated that billions of people in poor countries suffer from micronutrient deficiencies because they lack the money to buy enough meat, poultry, fish, fruits, legumes and vegetables. Women and children in sub-Saharan Africa, South and Southeast Asia, Latin America and the Caribbean are especially at risk of disease, impaired cognitive abilities and premature death because of diets poor in crucial micronutrients (McGuire, 1993).

The World Health Organization has shown that micronutrient deficiency is not exclusive to the developing world, having also been observed in developed countries. Of the most commonly studied micronutrients, iron, vitamin A and iodine are the ones most correlated with public health problems, both in Brazil and worldwide, although calcium, zinc, selenium and copper are also important for development (Kennedy et al., 2003).

Diets that lack iron and zinc can cause anaemia, reduced capacity for work, immunological problems, retarded growth and even death (WHO, 2000). Iron-deficiency anaemia is probably the most important nutritional problem in Brazil, affecting 30–80% of children aged five years and under, depending on the region and income, although this deficiency is independent of social class or geographic distribution. The most important iron sources in Brazil are common beans and red meat, with 1–7% of the iron they contain being absorbed by the body (Favaro, 1997).

Zinc deficiency has been less well studied but will also have a high incidence because the food sources for these two nutrients are the same. Zinc is required for the activity of more than 300 enzymes, many of which

act on the immune system and gene expression (McCall, 2000). Little is known about zinc deficiency in developing countries, although food sources that are rich in bioavailable iron are usually also rich in bioavailable zinc.

Vitamin A is essential for vision, growth and disease resistance. Vitamin A deficiency is a serious health problem in developing countries, causing blindness in children in 80 countries around the world. Increasing the intake of pro-vitamin A or carotenoids is one way of tackling this deficiency (Cozzolino, 2005).

Generally, there are three factors that cause variation in micronutrient levels in food: plant characteristics, such as age, degree of maturation, species, variety, cultivar and diet; environmental characteristics, such as climate, soil, rain and season; and processing parameters, such as storage, temperature, preservation method and preparation (Welch, 2001).

In developing countries, fortifying food with vitamin A and iron, and distributing supplements of these micronutrients to target populations, have been widely and successfully used to fight a lack of vitamin A and iron-deficiency anaemia (WHO, 1994). In regions with adequate infrastructure and well-established markets for delivering processed foods, such as salt, sugar and cereal flours, food fortification can greatly improve the micronutrient intake of vulnerable populations.

In Brazil, efforts in this direction started long ago by fortifying salt with iodine and adding fluoride to water in some regions. More recently, it has been mandatory to fortify wheat and maize flours with iron and folic acid to prevent anaemia and neural-tube defects, respectively (Cozzolino, 2005).

But there are limits to commercial fortification and supplementation. Fortified foods may not reach many of the people most in need because of poor market infrastructures. Supplementation also requires a good health infrastructure, a condition that is often lacking in developing countries. New approaches are therefore needed to ensure the wide availability of micronutrients in the diet.

Biofortification as an intervention strategy

The goal of biofortification is to help reduce the high prevalence of iron, zinc and vitamin A deficiencies by improving the micronutrient density of the staple food crops that are produced and consumed by low-income populations. Unlike traditional food fortification, biofortification does not require food to be processed centrally, as the micronutrients are already present in growing crops, making it more accessible to those who consume food that is grown locally, perhaps by themselves (HarvestPlus, 2008).

Biofortification is a long-term strategy aimed at increasing the micronutrient intake of large numbers of people throughout their lives, contributing to an overall reduction in micronutrient deficiencies in a population. However, it is not expected to treat severe micronutrient deficiencies or eliminate them in all population groups (HarvestPlus, 2008).

Even so, the introduction of biofortified crops will provide a sustainable and low-cost way of reaching people with poor access to formal markets or healthcare systems. Once the investment has been made in developing nutritionally improved varieties at central research locations, seeds can be adapted to the local growing conditions in numerous countries. Biofortified varieties can then provide benefits year after year throughout the developing world at a lower cost than either dietary supplements or fortification through food processing.

One way to ensure that farmers will like the new varieties is to give them a say about what traits are bred into the plants. Such participatory plant breeding, in which scientists take farmers' preferences into account during the breeding process, can be more cost-effective than confining breeding to research stations.

Preliminary research examining the feasibility of a plant-breeding approach for improving the micronutrient content of staple crops has made several important findings: substantial, useful genetic variation exists in key staple crops; breeding programs can readily manage nutritional quality traits, which for some crops are highly heritable and simple to screen for; the desired traits tend to be stable across a wide range of growing environments; and traits for high nutrient content can be combined with superior agronomic characteristics and high yields.

Where scientists can combine high micronutrient content with high yields, the nutritionally improved varieties are almost certain to be grown widely and marketed successfully. In fact, research showing that high levels of minerals in seeds also aid plant nutrition has fuelled expectations of increased productivity in biofortified strains.

Brazil's Biofortification Programs

HarvestPlus

The HarvestPlus Challenge Program on Biofortification was created to improve the nutritional quality of Brazil's main food crops, which can be adapted to suit the local growing conditions. It uses scientific and technological advances to improve the diet of some of the poorest populations in the world, who live on subsistence agriculture in the marginal zones of the tropics.

Initially, biofortification efforts will focus on six staple crops for which pre-breeding feasibility studies have been completed: beans, cassava, maize, rice, sweet potatoes and wheat. The program will also examine the potential for nutrient enhancement in 10 additional crops that are important components of the diets of people with micronutrient deficiencies: bananas/plantains, barley, cowpeas, groundnuts, lentils, millet, pigeon peas, potatoes, sorghum and yams.

The HarvestPlus objectives (HarvestPlus, 2004) are:

- Years one to four: 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 of 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 the 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 cost–benefit analyses of plant breeding and other food-based interventions to control micronutrient malnutrition.

- Years five to seven: Continue bioefficacy studies. Initiate participatory plant breeding and adapt high-yielding, conventionally bred, micronutrient-dense lines to particular regions. Release new conventionally bred biofortified varieties to farmers. Identify gene systems with the potential to increase nutritional value beyond traditional breeding methods. Produce transgenic lines experimentally 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
- Years eight to ten: 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 household resources, and the health effects on individuals

The HarvestPlus Challenge Program on Biofortification is an initiative of the Consultative Group on International Agricultural Research (CGIAR), which involves CGIAR research centers and partner institutions. It was planned for a 10-year period and is financially supported by the Bill and Melinda Gates Foundation and the World Bank, among others.

AgroSalud

The project "Combating Hidden Hunger in Latin America: Biofortified Crops with Improved Vitamin A, Essential Minerals and Quality Protein—AgroSalud" was intended to complement the HarvestPlus Challenge Program on Biofortification.

AgroSalud aims to reduce malnutrition and improve food and nutritional security in Latin America and the Caribbean through the consumption and production of biofortified crops and food products derived using traditional plant breeding methods. A specific objective is to reduce malnutrition caused by deficiencies in vitamin A, iron, zinc and protein in children and women of fertile age.

The main difference between the AgroSalud and the HarvestPlus programs is that AgroSalud focuses on Latin America and the Caribbean, and on post-harvest processing of crops that are important in the region, such as rice, beans, maize, cassava and sweet potato. Together with partners in different countries, AgroSalud carries out research in agronomy, nutrition, post-harvest technologies and social sciences to gather data that can be used to study the impact of biofortified crops and serve as a decision-making tool.

The AgroSalud objectives (AgroSalud, 2007) are:

- To develop, evaluate, disseminate and promote biofortified crops.
- To use traditional plant breeding methods to increase the contents of iron and zinc in maize, rice, beans and sweet potato, of tryptophan and lysine in maize, and of beta-carotene in sweet potato, cassava and maize.
- To measure the nutritional, economic and agronomic impact of these crops on producers and consumers.
- To determine the relevance and social, economic and financial viability of investing in the research and development of biofortified food products, as well as in their production, transformation and consumption.

The project, which is financed by the Canadian International Development Agency (CIDA), is led by five international organizations located in Brazil (the Brazilian Agricultural Research Corporation, Embrapa), Colombia (the International Center for Tropical Agriculture, CIAT; and the Latin American and Caribbean Consortium to Support Cassava Research and Development, CLAYUCA), Mexico (the International Maize and Wheat Improvement Center, CIMMYT) and Peru (International Potato Center, CIP). AgroSalud carries out work in Bolivia, Brazil, Colombia, Costa Rica, Cuba, Dominican Republic, El Salvador, Guatemala, Haiti, Honduras, Mexico, Nicaragua and Peru.

The HarvestPlus and AgroSalud programs were established in 2004 and are coordinated by Embrapa Food Technology, one of the research centers of the Brazilian Agricultural Research Corporation in Rio de Janeiro. The following research centers and institutions are also part of the Brazilian biofortification research net: Embrapa Rice and Beans, Embrapa Cassava and Tropical Fruits, Embrapa Maize and Sorghum, Embrapa Vegetables, Embrapa Mid-North, Embrapa Coastal Tablelands, Embrapa Wheat, Embrapa Soybeans, Embrapa Cerrados, Embrapa Tropical Semi-Arid, Embrapa Headquarters, Embrapa Office for Technological Innovation, the State University of Campinas (Unicamp), São Paulo State University (UNESP), the Federal University of Rio de Janeiro (UFRJ) and the Rural Federal University of Rio de Janeiro (UFRRJ).

The main objective of HarvestPlus is the identification of populations of cassava, common beans, maize, wheat and cowpea that have agronomic potential and higher levels of iron, zinc and pro-vitamin A than current crops. AgroSalud researchers study crops such as rice, sweet potato, common beans and cassava, and activities related to the post-harvest

processing of these biofortified crops are also carried out. In addition, pilot projects are underway for the dissemination of biofortified foods (including pumpkin) in the states of Maranhão and Sergipe in Northeastern Brazil.

The crops included in the program are already widely produced and consumed in Brazil, so farmers are already familiar with them and consumers do 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.

Another expected outcome of the biofortification programs is an integration of countries in Latin America, the Caribbean, Africa and Southeast Asia, with Brazil developing and transferring not only the biofortified varieties but also the technology for post-harvest processing. So far, Brazilian researchers have collaborated with colleagues in 10 African countries to develop local capacity for carotenoid analysis, and a practical training course on carotenoid detection and analysis was organized in Tanzania in July 2005.

Progress in some individual crops

Cassava

Cassava (Manihot esculenta) is a white-fleshed root crop, classified as sweet or bitter depending on the amount of cyanide-producing compounds. This perennial crop, native to South America, is a major source of provitamin A for people in Northeastern Brazil, sub-Saharan Africa and parts of Asia where drought, poverty and malnutrition are prevalent.

Breeding Activities

Embrapa Cassava & Tropical Fruits has been working on the biofortification of cassava since 2003. The strategy is to develop genotypes from agronomically superior varieties that have high concentrations of carotenoids in the roots and, with less extensive research, to breed for iron and zinc content.

The work started with the screening and breeding of cassava for carotenoids to select varieties by spectrophotometry. The total carotenoid content in the best varieties ranged from 6.4 μg per g to 15.5 μg per g. These varieties were used as parents for the development of new clones with a higher content of total carotenoids. In the first generation, some clones showed an increase of more than 140% in their total carotenoid content (relative to the parents); in the second generation, the increase was approximately 200%.

The first cassava varieties with a high content of carotenoids and a low content of cyanide were selected from the Embrapa Germplasm Bank and chosen by farmers and communities in a participatory breeding experiment in Northeast Brazil. These varieties were selected and planted in controlled areas and their clones were harvested and selected by their characteristics in 2007.

In early 2006, two yellow-rooted clones with higher levels of beta-carotene—Dourada (Golden) and Gema de Ovo (Egg Yolk)—were officially launched at a ceremony attended by more than 100 farmers. This event was the first step towards the release of nutritionally enhanced germplasm.

In early 2008, the beta-carotene concentration in the 2003 generation was evaluated. The average concentration of beta-carotene in the roots was 5.4 μg per g, ranging from 2.6 μg per g to 9.1 μg per g. There was no direct relation between the values of total carotenoids with beta-carotene. The levels of hydrogen cyanide, iron and zinc were also evaluated in the selected roots of hybrids from the 2003, 2004 and 2005 generations. The maximum levels of iron and zinc in the 2003 generation were approximately 51 mg per kg and 34 mg per kg, respectively. In the 2004 generation, the iron and zinc levels varied from 1.0 to 77 mg per kg and from 0.5 to 87 mg per kg, respectively. In the 2005 generation, the levels of iron and zinc varied from 20 to 30 mg per kg and from 2.4 to 34 mg per kg, and cyanide varied from 20 to 350 parts per million. These data result from studies on the roots of 10-month-old plants.

Other seedlings, acquired from a self-fertilization field with different varieties of cassava with high values of carotenoids, are being harvested. Their hybrids, which are an intense yellow colour, will be chosen and

planted to determine the value of total carotenoids, beta-carotene and cyanide.

The promising cassava roots, which have high levels of beta-carotene, iron and zinc, are being monitored in semi-arid regions of Brazil. A flour capable of conserving micronutrients is also being developed in partnership with Embrapa Food Technology. It could be used to produce bread, cake, pasta and other bakery products.

Carotenoid retention

Research has also been carried out at Embrapa Cassava & Tropical Fruits, in collaboration with São Paulo State University and the Federal University of Rio de Janeiro, to evaluate the retention of carotenoids in cassava roots and their by-products.

The retention of carotenoids was evaluated in different types of cassava flour (traditional flour, oven-dried 'scraping flour' (55°C) and 'gari flour' (fermented flour)) and chips. The gari flour, oven-dried 'scraping flour' and boiled root retained more carotenoids after processing. Regarding the time of storage, the sun-dried scraping flour and chips lost the least amount of carotenoids, although it was not possible to correlate carotenoid retention with the cyanide content of the fresh varieties or the obtained products.

The retention of beta-carotene and total carotenoids in yellow cassava varieties were evaluated both after traditional cooking and as flour. The highest retention of beta-carotene (79.8%) was observed when yellow cassava samples were cooked half-covered with water and boiled in a pot with the lid on; the retention of total carotenoids was greatest (81.5%) when the cassava were cooked completely covered with water and boiled in a pot with the lid on.

These preliminary studies have given the research team the opportunity to explore the relationship between the loss of total carotenoid content and beta-carotene content and genetic variation.

Sweet Potato

Africa's predominant sweet potato (*Ipomoea batatas*) cultivars are the white- and yellow-fleshed varieties, which contain small amounts of beta-carotene. In contrast, the orange-fleshed variety, although much less common, is a rich source of beta-carotene and can be grown year-round,

making it an ideal source of vitamin A. If sweet potato could be bred for local growing conditions, and if there were sufficient demand, farmers and consumers could switch to the orange-fleshed variety, increasing their vitamin A intake.

Breeding activities

Embrapa Vegetables has been working to increase the dry matter content of the provitamin A-rich orange-fleshed varieties to make them more palatable, as well as improving their resistance to viruses and environmental stresses. For the analyses, sweet potato genotypes, seeds and clones were imported from the International Potato Center (CIP) in Peru. Germplasm samples from the Embrapa Vegetables germplasm bank were screened, and orange-fleshed sweet potato samples were obtained from Brazilian farmers with the help of a popular television program.

Selected clones were evaluated for the productivity of their storage roots, amount of foliage, color, dry matter content, carotene content and flour productivity. The selected materials were planted again at low temperature to test their adaptability to severe climatic conditions, and the iron, zinc and carotene contents were evaluated.

The varieties sent by CIP were assayed and given nutritional evaluations in Maranhão and Sergipe, where field trials left them exposed to warm and rainy seasons. Six other clones with more than 100 mg per kg of beta-carotene were evaluated for beta-carotene, total and reducing sugar, starch content and sensory analysis.

Researchers are also developing ways of drying sweet potato plants without reducing the micronutrient content and of extracting the residue (bran) and the starch.

Post-Harvest Activities

Researchers from Embrapa Vegetables and Embrapa Food Technology have been working together to obtain flour from orange-fleshed sweet potato varieties. The flour was analysed for size and content of total carotenoids and beta-carotenes. Preliminary results show that the flour has good coloration and structure. French bread made with 15% sweet potato flour had a similar size to bread made with wheat flour; for sweet

breads, 20% sweet potato flour could be used; for other breads, 50% was the acceptable limit.

Processing sweet potato chips using 0.5–1.0% citric acid led to satisfactory results in preliminary tests, with the intense orange colour being maintained, especially after drying. Flaked instant puree is still being studied, but preliminary testing has revealed a homogenous appearance and intense orange colour, even after reconstituting with water.

These tests have shown how versatile orange-fleshed sweet potatoes are. They can be used as fresh roots, consumed boiled, roasted, fried and mashed, and used as an ingredient in various recipes. The processing of these roots into flour will allow it to be applied to social programs such as school lunches.

Common beans

An inexpensive bowl of beans is the centerpiece of the daily diet of more than 300 million people. Common beans (*Phaseolus vulgaris L.*) provide significant amounts of protein, complex carbohydrates and dietary fibre, as well as iron and zinc.

Protein energy undernutrition (PEU) remains a common problem in much of the developing world. More than one third of children less than five years of age in developing countries suffer from PEU, and the proportion of children who are undernourished has changed very little during the past 20 years. Given the widespread consumption of beans throughout the world, efforts to improve their micronutrient content could potentially benefit large numbers of people.

Researchers are trying to endow common bean seeds with higher levels of iron and zinc, with the aim of doubling the quantity of these minerals to 50 p.p.m. for zinc and 100 p.p.m. for iron. If this can be achieved, the biofortified beans will provide much of the mineral requirements of the malnourished people in Northeastern Brazil.

Breeding activities

Researchers at Embrapa Rice and Beans have been developing biofortified common beans in the Brazilian states of Goiás and Pernambuco. Their research is focused on increasing the concentrations of iron and zinc in agronomically superior cultivars, specifically those tolerant to drought

and adapted to the environment in Northeastern Brazil. But first the Grain Quality laboratory required the purchase of an atomic absorption spectrophotometer and a ball mill. The scientists also improved the mineral analysis methodology, based on the AOAC method with modifications by the Waite Agricultural Research Institute of the University of Adelaide in Australia, and other adaptations were made to avoid iron contamination.

Traditional cultivars, breeding cultivars, landraces and accessions from Embrapa's germplasm bank and CIAT's core collection were planted for multiplication during winter, under irrigation, in Santo Antônio de Goiás, Porangatu and Petrolina. These genotypes were harvested, sampled and sent to Embrapa Rice and Beans, where the average iron and zinc levels were found to be 76 p.p.m. (ranging from 40 to 130 p.p.m.) and 26 p.p.m. (ranging from 7 to 58 p.p.m.), respectively. The best accessions were used as parents in crosses to select genotypes with high levels of iron and zinc, which were included in commercial groups of beans. All the iron and zinc results were validated at Embrapa Food Technology in Rio de Janeiro. Based on these results, Embrapa Rice and Beans has chosen two cultivars, BRS-Marfim and BRS-Pontal, for a pilot study; their iron and zinc contents were found to be around 80 p.p.m. and 45 p.p.m., respectively.

Research into the drought resistance of common beans has been underway since 2006. The first experiments were carried out in Santo Antônio de Goiás and Porangatu in Goiás state. Pre-selected genotypes were planted and either properly irrigated or given insufficient water. After harvesting, the grains were analyzed for iron and zinc.

At the end of the experiment, genotypes that presented good yields of iron and zinc without water stress were selected, along with those that were less susceptible to water stress.

These trials were repeated to confirm the adaptability and stability of mineral contents in different locations and environmental conditions. It was found that iron and zinc absorption by common beans is not strongly affected by water stress. The productivity of 81 genotypes and 20 populations with a high iron content planted in Porangatu was also investigated. In 2007, Porangatu suffered a severe drought, providing seven germplasms with drought tolerance; these were also evaluated for iron and zinc contents.

A new trial was planned in 2008 to select drought-tolerant samples. The genotypes used were selected from five sources: a nursery of samples grown under drought and high-temperature conditions; the CIAT Core Collection; new cultivars; Brazilian landraces; and a phenotype trial. The results are still preliminary, although, some cultivars already appear to be drought tolerant, such as BRS Pontal (iron level of 80.2 p.p.m. and zinc level of 49.6 p.p.m.) and BRS Agreste (iron, 78.8 p.p.m. and zinc, 45.6 p.p.m.).

These trials have yielded promising genotypes with high iron and zinc contents, good yield performance and less susceptibility to water stress, and some of these will be fast-tracked into use in Brazil.

Mineral retention

Research carried out at Embrapa Food Technology in collaboration with the Federal University of Rio de Janeiro sought to evaluate the retention of iron and zinc in common bean cultivars after cooking. The iron and zinc contents of raw and cooked grains were evaluated, along with various varieties of beans used in broth prepared according to traditional Brazilian cooking methods. The levels of iron and zinc in cooked beans were dependent on the cooking method. When the beans were immersed in water and cooked in a pressure cooker, the iron contents in the broth are significantly higher than when the beans are cooked in a Teflon pan with the lid partly open. In contrast, the zinc content was preserved in cooked grains regardless of whether the beans were previously immersed in water or not or cooked in a pressure cooker or a Teflon pan. Most of the iron and zinc remaining in the beans after cooking was concentrated in the kernels, so to maximize the mineral intake, it is important to consume the cooked beans in the broth.

Evaluating nutrition

One aim of the nutrition studies in Brazil is to evaluate the potential of biofortified crops in school meals in two Brazilian states where micronutrient deficiencies are particularly prevalent. The studies are being carried out in partnership with the Brazilian Ministry of Health and with the support of the National Fund for School Development (FNDE/MEC), the agency responsible for school meals in Brazil. The micronutrient

deficiency was identified, and the distribution program established, on the basis of data from the National Research of Demography and Health (PNDS), the Budget Family Research (POF) and the Feed and Nutrition System Monitoring (SISVAN), among other sources.

The state of Maranhão in Northeastern Brazil was chosen for a pilot project for three reasons: it has a high level of malnutrition (42%), low coverage from supplementation programs (vitamin A and iron), and high agricultural potential. The nearby state of Sergipe has similar nutritional problems to Maranhão and was also included in the study.

The project nutritionists went to São Luis, Icatu and Chapadinha in Maranhão, and Aracaju, the capital of Sergipe, where meetings were organized with administrative agencies and local institutions responsible for agriculture, education and health in order to present the objectives of the AgroSalud program. In Maranhão, partnerships were established with representatives of universities (the Federal University of Maranhão and the private university centers of Maranhão), the National Food Security Council (CONSEA) and the state's Health Secretary. In Aracaju, a work plan was developed in collaboration with the Federal University of Sergipe and Embrapa Coastal Tablelands

While the nutritionists were in Maranhão and Sergipe, they also collected data on iron and vitamin A deficiencies in the target sites, explored the governmental programs set up to prevent these deficiencies, conducted research about cooking and food preparation methods, evaluated possible partnerships with non-governmental organizations, evaluated the local production of the project's target crops (cassava, maize, rice, beans and sweet potato), evaluated the logistics of food distribution in the area and collected data on the local eating habits. They also discussed the possibility of establishing partnerships with local programs, including the National School Lunch Program (PNAE) and the Food Acquisition Program (PAA). In both states, they established a partnership with the representatives of Brazil's National Commodity Supply Agency (CONAB). Despite this, the logistics strategies will be defined after the sensory evaluation tests (for palatability), which will be carried out with school and pre-school children in 2009 in Maranhão e Sergipe.

The sensory evaluation requires the authorization of the local Ethics Committee and the local Education Secretaries and the training of volunteers and meetings with parents and school directors. Agreements have been signed in Maranhão and Sergipe for work to start and to raise funds.

Sergipe and Maranhão are not only home to these studies but are also the expected location of a 'biofortified food channel'. Agrosalud will evaluate the agronomical performance of biofortified crops in the region, assess the acceptability of the biofortified crops to local producers and children, and explore the way the biofortified crops are integrated into the local diet.

Conclusion

Many developing countries lack the distribution systems to reach the poorest people. With biofortification, the distribution network is less of a problem. When households grow micronutrient-rich crops, the biofortified foods are already in the hands of the people who need them; there is no need to have them delivered. Little intervention or investment is needed once local farmers have adopted the new seed. Moreover, micronutrient-rich seed can easily be saved and shared by even the poorest households.

The ultimate solution to eradicating undernutrition 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. In the meantime, biofortification makes sense as part of an integrated food-systems approach for reducing undernutrition. It addresses the root causes of micronutrient malnutrition, targets the poorest people, uses built-in delivery mechanisms, is scientifically feasible and cost-effective, and complements existing interventions to control micronutrient deficiencies. It is an essential first step in enabling rural households to improve their nutrition and health in a sustainable way.

Embrapa has valuable experience in the development and promotion of local systems for distributing seed, thanks to its 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 seed enterprises will play a crucial role in getting micronutrient-rich varieties into the hands of growers on the ground.

The results presented here are the consequence of the hard work of more than 150 people in different regions of the country who sought to achieve the objectives of HarvestPlus and AgroSalud.

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Global Status and Prospects of Commercialized Biotech Crops

Clive James

The International Service for the Acquisition of Agri-biotech Applications (ISAAA) is a non-profit charity registered in the United States and sponsored by both public- and private-sector organizations. Its mission is to alleviate poverty by sharing knowledge on crop biotechnology freely with the global society while respecting its right and independence to make decisions based on that knowledge. Thus ISAAA facilitates the three–steps process of knowledge, crop biotechnology and the alleviation of poverty, particularly for small, resource-poor and subsistence farmers in the developing world, who represent approximately half of the world's poorest people. Here I will examine the adoption and impact of biotech (genetically modified) crops during their first 12 years of commercialization, from 1996 to 2007, and discuss their future prospects.

The growth of biotech crops

The consistent and substantial benefits of biotech crops during the first dozen years of commercialization, from 1996 to 2007, have led farmers to plant more biotech crops every single year. In 2007, for the twelfth consecutive year, the global area of biotech crops continued to soar, with a sustained growth rate of 12%, or 12.3 million hectares—the second-highest increase in global biotech crop area in the past five years—reaching a global total of 114.3 million hectares (Figure 1).

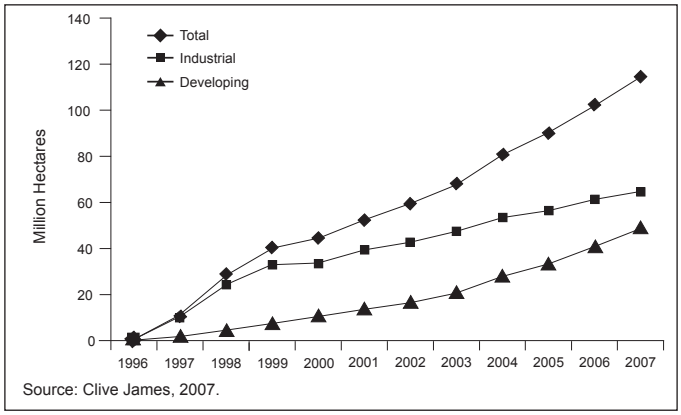

Figure 1 Global Area of Biotech Crops From 1996 to 2007 in Industrial and Developing Countries.

Many biotech crops have two or three 'stacked traits', which confer multiple benefits in a single biotech variety. For this reason it is common to give figures in 'trait hectares', rather than hectares, so for example a hectare of a crop with three stacked traits would count as three trait hectares—this is similar to measuring air travel in 'passenger miles' rather than miles. Growth measured in trait hectares between 2006 (117.7 million) and 2007 (143.7 million) was 22%, or 26 million trait hectares. This is approximately twice the apparent growth when conservatively measured in hectares of only 12%, or 12.3 million hectares.

In 2007, the number of countries planting biotech crops increased to 23, comprising 12 developing countries and 11 industrial ones. In order of hectarage, these are the United States, Argentina, Brazil, Canada, India, China, Paraguay, South Africa, Uruguay, the Philippines, Australia, Spain, Mexico, Colombia, Chile, France, Honduras, Czech Republic, Portugal, Germany, Slovakia, Romania and Poland. The first eight of these countries grew more than 1 million hectares each. The strong growth across all continents in 2007 provides a broad and stable foundation for future global growth. The two new countries to take up biotech crops in 2007 were Chile, which produced more than 25,000 hectares of commercial biotech crops for seed export, and Poland, a European Union country that started planting *Bt* maize, which contains a gene from the soil bacterium

Bacillus thuringiensis that produces an insecticide to protect the plant from insect damage.

The cumulative area of biotech crops from 1996 to 2007 exceeded two–thirds of a billion hectares (690 million hectares acres), with a 67–fold increase between 1996 and 2007, making it the fastest-adopted crop technology in recent history. This high adoption rate by farmers reflects the fact that biotech crops have consistently delivered significant economic, environmental, health and social benefits to both small and large farmers in developing and industrial countries. It can be seen as a strong vote of confidence from farmers in 23 countries over a 12–year period who made approximately 55 million individual decisions to plant biotech crops, year after year, after gaining first-hand experience with biotech crops on their own or a neighbour's fields.

In 2007, the United States, Argentina, Brazil, Canada, India and China continued to be the principal adopters of biotech crops globally (Figure 2). The United States remained the top grower with 57.7 million hectares (50% of the global biotech area), spurred by a growing market for ethanol, as the biotech maize area increased by a substantial 40%, which was partly offset by smaller decreases in biotech soybean and cotton. But 63% of biotech maize, 78% of biotech cotton and 37% of all biotech crops grown in the United States in 2007 were stacked products containing two or three traits delivering multiple benefits. Stacked products are an important feature and future trend that meets the multiple needs of farmers and consumers. They are now increasingly grown in 10 countries: the United States, Canada, the Philippines, Australia, Mexico, South Africa, Honduras, Chile, Colombia and Argentina, and more countries are expected to adopt stacked traits in the future.

Biotech crops achieved an important milestone in 2007 with humanitarian implications, as the number of small and resource-poor farmers benefiting from biotech crops in developing countries exceeded 10 million for the first time. Of the global total of 12 million farmers who grew biotech crops in 2007 (up from 10.3 million in 2006), more than 90% (11 million, up significantly from 9.3 million in 2006) were small and resource-poor farmers from developing countries; the remaining 1 million were large-scale farmers from both industrial countries such as Canada and developing countries such as Argentina. Of the 11 million small farmers, 7.1 million

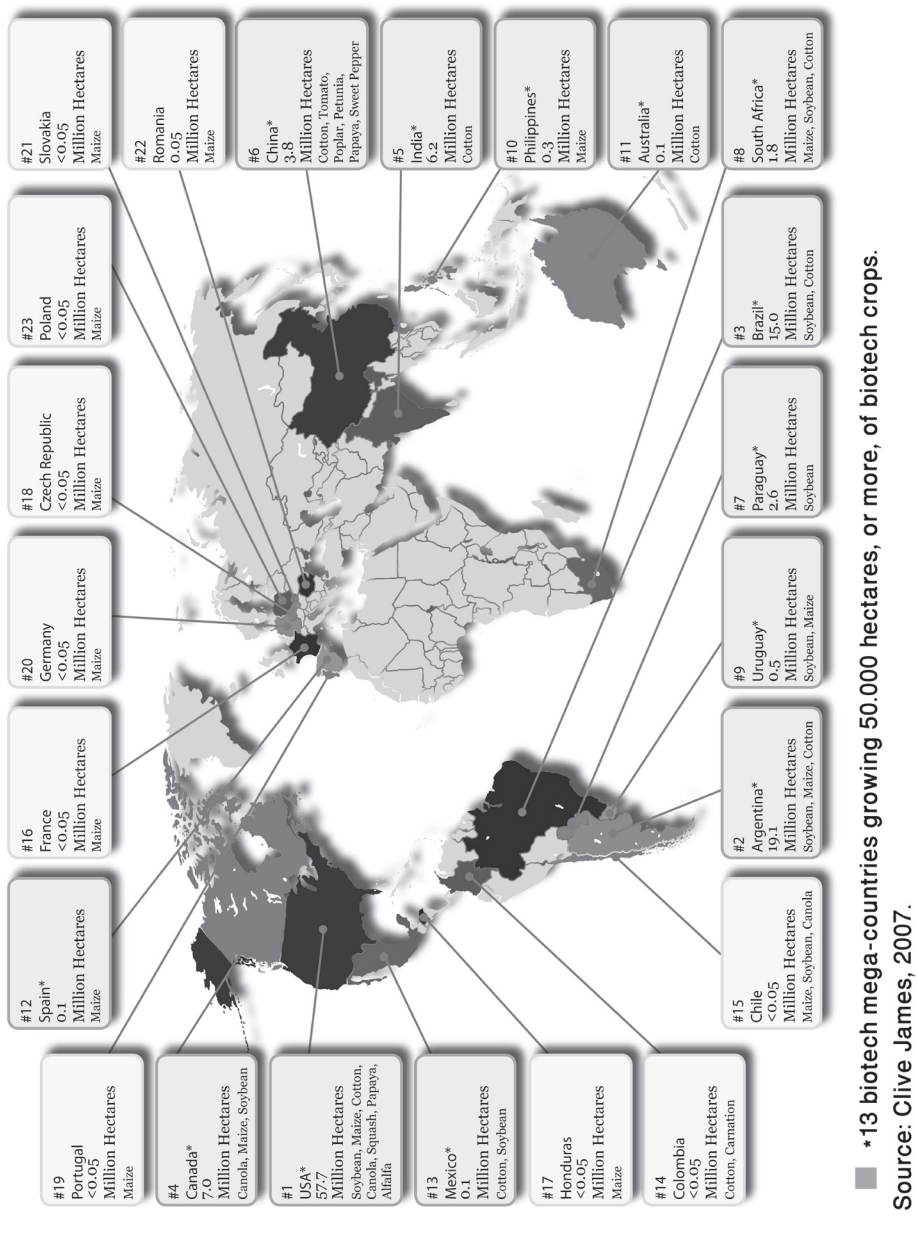

Figure 2 Biotech Crop Countries and 'Mega-Countries' (Countries That Grow 50,000 Hectares or More) in 2007.

in China grew *Bt* cotton, 3.8 million in India also grew *Bt* cotton, and the remaining 100,000 were in the Philippines (biotech maize), South Africa (biotech cotton, maize and soybeans, often grown by subsistence women farmers) and the other eight developing countries. This initial modest contribution of increased small-farmer income from biotech crops is a very encouraging step towards the Millennium Development Goal of reducing poverty by 50% by 2015. There is enormous potential for increase in the second decade of commercialization, 2006 to 2015.

From 1996 to 2007, the proportion of the global area of biotech crops grown by developing countries increased consistently every single year. In 2007, 43% of the global biotech crop area (up from 40% in 2006)—equivalent to 49.4 million hectares—was grown in developing countries, where growth between 2006 and 2007 was substantially higher (8.5 million hectares, or 21% growth) than industrial countries (3.8 million hectares, or 6% growth). The five main developing countries committed to biotech crops span all three continents of the South; they are India and China in Asia, Argentina and Brazil in Latin America, and South Africa on the African continent. Collectively they represent 2.6 billion people, or 40% of the global population, with a combined population of 1.3 billion who are completely dependent on agriculture. These include millions of small-scale and resource-poor farmers and the rural landless, who represent the majority of the poor in the world. The increasing collective impact of the five principal developing countries is an important trend that has implications for the future adoption and acceptance of biotech crops worldwide.

Impact of biotech crops

From 1996 to 2006, biotech crops led to improved productivity and income, with yields increasing by 5–50%. Farm income from biotech crops rose by US$7 billion in 2006, and US$34 billion over 1996 levels, with US$17.5 billion in industrial countries and US$16.5 billion in developing countries (Brookes and Barfoot, 2007).

Crop production was doubled in the same area on 1.5 million hectares of crop land. This saves forests and aids biodiversity, as 13 million hectares of forest are lost every year in developing countries.

In terms of environmental input, biotech crops saved the use of 289,000 tonnes of pesticide from 1996 to 2006. They also saved 15 billion kg of carbon dioxide in 2006, which is equivalent to having 6.5 million fewer cars, helping to mitigate climate change. They also helped to conserve soil and water, which aids sustainability. In addition, biotech crops helped to alleviate the poverty of 11 million small farmers in 2007, compared with 9.3 million in 2006, and led to more affordable food, feed, fibre and fuel.

Future prospects

The prospects of biotech crops during the second decade of commercialization, from 2006 to 2015 (the year of the Millennium Development Goals), are looking bright. In particular, continued growth is expected in the United States, Canada and Australia, with an expanded range of biotech crops featuring more agronomic and quality traits, plus the important trait of drought tolerance, which is expected in about five years. The adoption of biotech crops will be boosted by high commodity prices.

The first decade of commercialized biotech crops, from 1996 to 2005, was the decade of the Americas. The second decade is likely to feature strong growth in Asia, led by India, China and new countries to biotech crops, such as Vietnam and Pakistan. Biotech rice will become the most important crop to be commercialized globally. It has already been extensively field-tested in China and is capable of delivering benefits estimated at US$4 billion per year.

In Africa, the number of countries growing biotech crops is expected to increase, led by Egypt in North Africa, Burkina Faso in West Africa, and Kenya in East Africa. There will be slow to modest growth in the European Union, with Eastern Europe having the most potential.

Biotech crops will increasingly be grown for biofuel—ethanol and biodiesel—led by the United States and Brazil. This is likely to help Brazil become the leading grower of biotech crops in Latin America.

Conclusions

As a result of consistent and substantial economic, agronomic, environmental and social benefits during the first dozen years of commercialization, from 1996 to 2007, farmers have continued to plant more biotech crops every single year. In 2007 there was 12% growth (an extra 12.3 million hectares), bringing the total area of biotech crops to 114.3 million hectares. Biotech crops have already helped to alleviate poverty, and this is set to continue, as the prospects from 2008 to 2015 are very encouraging.

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17

Effect of *Bt* Corn on Infestations of Corn Borers in Egypt

Magdy A. Massoud

Corn (maize) is a major food staple across the world and is one of the best grain sources of easily metabolized energy (Wright, 1988). Developing countries cultivate two-thirds of the world's maize by area (James, 2003). However, it is prone to damage from insects, which feed on the leaves, tunnel into the stalk and damage the leaf sheath, collar and ear. The main pest worldwide is the larva of the corn borer, *Ostrinia nubilalis*, which tunnels into the stalk, although another corn borer, *Sesamia cretica*, is the chief culprit in Egypt. The corn borer is hard to treat economically with conventional chemicals, not least because it is hard to know when to apply the insecticide to protect the crop across the entire egg-laying period (Tollefson and Calvin, 1994). In the United States alone, the corn borer causes yield losses of 3–7% per borer per plant, leading to annual losses of between US$37 and US$172 per hectare of corn (Sanders et al., 1998). Roughly 9% of the world's maize crop is lost annually to insect pests, representing a total cost of US$5.7 billion, and a further US$550 million is spent on insecticides (James, 2003).

One option is to use transgenic corn that has been genetically modified to express the cry1Ab gene from the soil bacterium *Bacillus thuringiensis*. The corn then produces the Cry1Ab protein, which is toxic to insects. When the crystalline protein is solubilized in the insect's midgut, it releases endotoxins that are activated by the insect's midgut proteases. The activated

toxin disrupts the integrity of the larva's midgut epithelium, killing the insect.

Cry1Ab has been used as the active ingredient in *Bt* insecticides for many years. In *Bt* corn, the Cry1Ab protein produced is rapidly degraded in the soil and has no effect on soil microbial populations or non-target organisms (Head, 2007). Its action is specific to lepidopteran insects because they have Cry1Ab-specific receptors in their midgut (Van Rie et al., 1990). Mammalian intestinal cells do not have receptors for the endotoxins, so Cry1Ab is not toxic to humans or other mammals (Noteborn et al., 1995).

Bt corn (MON 810) suffers much less insect damage than normal corn, as the Cry1Ab protein provides effective protection from corn borers throughout the growing season (Massoud, 2005). But the *Bt* gene confers even more advantages. Tunnelling by the corn borer is one of the main pathways by which the fungus *Fusarium moniliforme* infects corn (Munkvold et al., 1997). *Fusarium* produces fumonisin, a mycotoxin that is hazardous to animals and humans (Sobek and Munkvold, 1999). *Bt* corn suffers less tunnelling and so has a lower occurrence of fungal infection and contains less mycotoxin (de la Campa et al., 2005).

In 2006, 91.0 million hectares of *Bt* crops were planted, of which 11.1 million hectares were *Bt* maize (James, 2006). This rapid spread can be attributed to a variety of factors, but key among these is the ability of growers to protect crop yield. The increased yield for *Bt* corn has been reported to be as high as 26%, depending on the region (Economic Research Service, 1999).

Maize crop in Egypt

Maize is the second most important cereal crop in Egypt behind wheat. In recent years, the total area planted with maize in Egypt, in the summer and Nili seasons (from mid-August to late November) together, is about 850,000 hectares. Of this, 86% is planted in summer, with just 14% planted in the Nili season. About 90% is white maize, the rest being yellow maize. Almost 96.5% of the total area cultivated with maize is along the Nile valley.

Bt maize (Ajeeb-YG) is genetically modified to provide season-long protection against stalk borers, such as *S. cretica*, *O. nubilalis* and *Chilo agamemnon*. It has been tested in Egypt since 2002, and was recently authorized for commercial release. *Bt* maize (MON 810) also provides effective protection, with high specificity against pests. Both lines of *Bt* corn provide significant benefits for farmers, consumers and the environment. In addition to a higher yield, the *Bt* technology also results in reduced use of insecticides, lower potential exposure to insecticide, improved stalk lodging resistance, improved grain quality, lower levels of mycotoxins, increased numbers of beneficial insects relative to insecticide-treated fields, and greater flexibility in planting time. For Egyptian farmers, using *Bt* maize seems an easy decision to make.

Maize pests in Egypt

Stalk borers are considered the major pests of maize and are the focus of most integrated pest management (IPM) programs (Ferro and Howell, 1985). Their larvae feed on all the above-ground maize tissues, and the tunnels they make compromise the movement of nutrients and water, and weaken stalks and shanks, often causing lodging or ear drop, especially in the wind (Witkowski and Wright, 1997). Tunnelling also leaves the plant vulnerable to fungi, which has health implications for both humans and livestock (Hyde et al., 1999).

The pink stem borer, *S. cretica*, the European maize borer *O. nubilalis* and the mole cricket, *Gryllotalpa spp.*, are the three pests with the greatest effect on maize productivity in Egypt. Egypt's Agricultural Research Center has an active breeding program to develop maize hybrids that are tolerant to the pink stem borer, as this is seen as the most damaging of the three.

Chemical control of stalk tunneling lepidopteran larvae is largely ineffective, and less than half of Egypt's maize growers use chemical insecticides to control corn borers. The main chemical used is the organophosphate diazinon, but it must be applied at least four times depending on the level of infestation. Spraying usually starts 21 days after planting and is repeated every two weeks until the growth stage V10 (just before tasselling).

Controlling infestations of corn borers

In Egypt, seedlings are the most easily damaged corn stage. Protecting them from borers is important because an adequate plant population during this stage is essential for the farmer to obtain a good yield later. Once the plant has been damaged, there is little that can be done to help it recover. *S. cretica* attacks maize earlier in its growth stage than the other two species, but it can also be destructive in the pre-harvest stage as well, even after diazinon treatment. Mesbah et al. (2002) observed that the sowing dates have a role in the incidence of stem borer infestation throughout the growing season. Female *C. agamemnon* moths begin laying eggs on corn plants that reach 100–120 cm height (or are about 40–45 days old). Mote (1986) found that the highest percentage of stem tunnelling by Chilo occurred in Indian sorghum sown on 1 June, and the lowest was observed in the crop sown on 15 August. Late-season populations of *O. nubilalis* prefer to oviposit on corn that is at or near the pollen-shedding stage, so late-planted corn is more attractive to the moths than adjacent older stands (Witkowski and Wright, 1997). So early planting can reduce damage from *O. nubilalis*, but later sowing dates may avoid damage from *C. agamemnon* and *S. cretia*. There is no planting date that will effectively avoid the worst damage from all three of the stalk borers.

Three years of data from Egyptian maize trials has shown that diazinon treatment has only a modest influence in controlling damage from the three stalk borers. The highest figures for the reduction of damage from *S. cretia*, *C. agamemnon* and *O. nubilalis* were 70%, 52% and 54%, respectively. At many survey times for all three species, diazinon-treated crops did not differ significantly from untreated conventional hybrids.

In sharp contrast, MON 810 *Bt* corn was almost completely protected from damage by stalk borers. Infestations of *S. cretica*, *C. agamemnon* and *O. nubilalis* were negligible or completely prevented in *Bt* plants throughout the whole season for all sowing dates (an infestation reduction of 90–100%). What little damage there was, consisted of a few failed attempts by larvae to bore inside the plant. In these instances, no larvae, alive or dead, were found within the stalks.

Effect on the yield

Across the three seasons studied by Massoud (2009a), plant height and ear position appeared to be slightly influenced by planting date, but not by variety type. The number of ears per plant was affected by the presence of the *Bt* gene only four times among the eleven planting dates studied. In 2002, *Bt* maize produced significantly more ears per plant than the untreated conventional version for all three planting dates. In 2004, for corn planted in June, *Bt* maize had more ears per plant than either the untreated or diazinon-treated versions.

The main influence of the *Bt* gene was reflected in the yield, in terms of the field weight and adjusted grain yield. Both field weight and adjusted grain yield increased significantly in *Bt* maize over non-*Bt* plants (diazinon-treated or untreated) across all planting dates over the three seasons studied.

Incorporating the *Bt* gene (MON 810) in corn provides season-long protection from stalk-boring lepidopterans, regardless of planting date. This protection leads to significantly increased yields, even over insecticide-treated conventional hybrids, and the *Bt* gene has little effect on other agronomic characteristics such as plant height or ear position.

Bt corn provides a range of benefits:

- Protects the corn from pests, leading to higher yields
- Controls target insects but does not harm beneficial species
- Eliminates the need for expensive chemical insecticides
- Reduces exposure to chemical pesticides
- Fits in with integrated pest management and sustainable agricultural systems
- Reduces the level of mycotoxin in corn kernels
- Requires no additional labour or machinery requirements, allowing both large and small growers to maximize the yield (Rice and Pilcher, 1999)

Given the absence of a clear strategy for planting dates, the poor performance of conventional chemical control, and the high and uniform efficacy of *Bt* MON 810 maize on all three of Egypt's main stalk borers, Egyptian maize production would almost certainly benefit greatly from the widespread adoption of *Bt* maize. I propose that corn germplasm containing *Bt* MON810 is a good tool for controlling corn borers and deserves a place at the forefront of IPM for corn in Egypt.

Preventing insect resistance

There is a risk that stalk borers could develop resistance to the Cry1Ab protein produced by *Bt* corn. Farmers who cultivate *Bt* corn should therefore plant a refuge of non-*Bt* corn to ensure that the benefits are maintained in future years. It is recommended that at least 20% of the total maize in an area should be non-*Bt* maize. This guideline should be strictly followed and implemented on large commercial farms, but it may be impractical on small farms.

Integrated pest management relies on a combination of ways to decrease the pest problem in the crop, over seasons and years, not just during crop cultivation. Some natural alternatives, such as letting weeds grow nearby or planting other crops, can help maintain wild-type insect populations. A two-year study in the Nile Delta to compare the survival of larvae of the three stalk borers on different cultivated and wild plant species found that they could all live on at least five plant species during the summer cropping season (Massoud, 2009b). Planting such species will help to stop the insects from developing resistance to *Bt* corn.

The host plants for *Sesamia cretica* are: maize (*Zea mays*); sweet sorghum (*Sorghum vulgaris* var. *saccharatum*); broom sorghum (*Sorghum vulgaris* var. *technicum*); sugarcane (*Saccharum officinarum*); common reed (*Phragmitis communis*); and elephant grass (*Pennisetum purpureum*).

The host plants for *Ostrinia nubilalis* are: maize (*Zea mays*); sweet sorghum (*Sorghum vulgaris* var. *saccharatum*); broom sorghum (*Sorghum vulgaris* var. *technicum*); common reed (*Phragmitis communis*); sharp pointed rush (*Cyperus alopecuroides*); pepper (*Capsicum annuum* L.); tomato (*Lycopersicon esculentum* Mill); and potato (*Solanum tuberosum* L.).

The host plants for *Chilo agamemnon Bless* are: maize (*Zea mays*); sweet sorghum (*Sorghum vulgaris* var. *saccharatum*); broom sorghum (*Sorghum vulgaris technicum*); sugarcane (*Saccharum officinarum*); common reed (*Phragmitis communis*); rice (*Oryza sativa*); barnyard grass (*Echinochloa crus-galli*); and cabbage (*Brassica oleracea* var. *capitata*).

The data support the idea that alternative hosts can be used as a refuge to dilute the development of insect strains resistant to the Cry1Ac protein. In addition to these plant species, other maize types that do not contain the *Bt*

gene, such as white maize hybrids and non-*Bt* yellow hybrids, will continue to be widely distributed in the main maize-producing areas of Egypt after commercialization. Cropping and intercropping of these alternative plant species will provide sufficient refuges to maintain susceptible populations of borers, which would mate with potential resistant strains that could arise in fields of *Bt* corn.

Conclusions

The major pests of maize in Egypt are the pink corn borer (*Sesamia cretica*), the purple-lined corn borer (*Chilo agamemnon*) and the European corn borer (*Ostrinia nubilalis*), which tunnel into the tassel, ear, ear shank and stalk to feed. Controlling stalk-tunnelling lepidopteran larvae with conventional chemicals is difficult.

Bt maize (Ajeeb-YG) is genetically modified to produce the Cry1Ab protein, which gives it whole-plant, season-long protection against stalk borers. It has been tested in Egypt since 2002 and has recently been authorized for commercial release. Similarly, *Bt* MON 810 maize exhibits almost complete protection from damage by all the three borer species. The reduction in infestation was 90–100% for *Bt* maize throughout the season for all sowing dates. This insect protection led to much higher yields, even compared with insecticide-treated conventional maize, and the *Bt* gene had little or no effect on other agronomic characteristics measured.

Some natural alternatives, such as the presence of weeds or other crops, may help to manage the development of insect resistance by maintaining wild-type insect populations. The data collected in Egypt show that the three stalk borer species can be found on different plant species that coexisting with maize during the summer cropping season. These alternative hosts can be used as refuges to dilute the development of insect strains that are resistant to Cry1Ac.

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18

The Future for Phosphorus in World Agriculture

Ewald Schnug and Silvia Haneklaus

Few words have been abused as often as the term 'sustainability'. In some cases, sustainability is viewed as being synonymous with profitability, but economic return is definitively not an indicator of sustainability. Various sectors of society around the globe have been profitable, but we are far from being on the road towards sustainable development. Industrialization has provided innumerable commodities, amusements and even some satisfaction, but it has become increasingly alienated from families, communities and the natural world. In the rush to make profits, the true meaning of sustainable development is often forgotten (Ekardt, 2005). In 1987 the Brundtland Commission defined sustainable development as: 'Development that meets the needs of the present without compromising the ability of future generations to meet their own needs.' This implies that investment in sustainability is an asset for future generations.

Agriculture is globally indispensable for food production, but climate change will affect food security. As the supply of fossil fuel declines, fertilizers and pesticides may become less available, or at least much more expensive, leading to reduced application and a potentially negative impact on crop yields (Lee et al., 2008). It may also become more expensive, or even unviable, to transport food more than just a few kilometres. Pesticides may also compromise food safety as they can contaminate food, migrate into groundwater and have a variety of negative effects on soil life and other ecosystems.

The use of fertilizers can provide agricultural crops with essential plant nutrients, and harmonised nutrition is a prerequisite for maintaining crop productivity, crop quality and plant health. But fertilizers can significantly reduce sustainability by the pollution of the atmosphere and water bodies with nitrogen compounds, the loss of nitrogen and phosphorus from agro-ecosystems, the waste of non-renewable phosphorus through inefficient fertilization strategies, the charging of soils with heavy metals and radioactivity through the application of waste materials and phosphorus-based fertilizers, and the contamination of soils with hazardous organic compounds, pharmaceuticals and infectivity. Consequently, it is a prime task of science to develop and verify strategies that can avert these undesirable side effects or at least reduce them to an unavoidable minimum.

The promise of sustainability

Essential compounds such as vitamins and minerals, and hazardous contamination with inorganic heavy metals or organic pollutants such as pesticides and mycotoxins, are important quality criteria and can have a significant impact on people's health, quality of life and even lifespan. Today's agriculture suffers from issues such as health problems caused by pesticides, antibiotics or the hormones used in animal husbandry, environmental burdens caused by pesticides and agrochemicals, pollution by animal manure and organic waste products, and diminished biodiversity in ecosystems, including agricultural production.

Food quality is also dependent on the way food is produced (the process quality). There are basic differences in process quality between conventional and organic production systems (Schnug, 2003; Schnug et al., 2006a). Organic farming is a well-defined production concept (Schmidt and Haccius, 1998) that provides practical solutions to various problems of agricultural production and reinforces environmental protection and nature conservation, thereby meeting the demand for sustainability (Schnug et al., 2006a). In organic farming, the impact of agricultural production on other ecosystems and organisms involved in the production system, such as animal welfare, is assessed. Organic management is possible on arable farms too, although livestock is often a crucial part of the system,

as manure and slurry contribute significantly to the maintenance of closed nutrient cycles. This aspect is particularly important for nutrients such as phosphorus (P) for which natural resources are limited.

The role of phosphorus

Phosphorus is a non-renewable reserve that will be depleted in about 100 years. Although P resources are much higher than the actual P reserves, access to P is likely to be increasingly restricted by economic constraints.

Agriculture is the largest user of phosphates and also the largest source of phosphate losses by environmental dispersion (as a result of surplus enrichment in soils and erosion) and irreversible fixation (bone meals and ash). The export of P in the form of feedstuff by developing countries will contribute to the problem of P mining in these regions, while enhancing P stocks in industrial countries. In addition, the spread of biofuel plants has been reinforced in industrial countries as a counter-measure against increasing energy costs and is a contribution to lessening the burdens of climate change. The switch to biofuels has global impact, not only on the environment, but also on food security and food prices. Increasing product prices in the non-food sector will not only promote the conversion of natural land, forests and grasslands into agricultural land globally, but also intensify plant production in the non-food segment. The greater use of fertilizers will diminish the efficiency of nutrient use and may increase nutrient losses to the environment, contributing for instance to the eutrophication of water bodies, as the higher nutrient levels trigger increased primary productivity.

From the viewpoint of plant nutrition and soil science, the acceptable level of surplus P on soils that already have sufficient P (80 mg of extractable P per kg, based on studies on lactic acids in Germany) can be set close to zero because, in biologically active soils, P from fertilizers can be fully utilised by plants, given infinite time and a mineral P source that is soluble in citric acid.

The spatial speciation of nutrients is important too. For instance, the limitation of soil P tests as a tool for integrated P management is that information gained from soil testing is discrete in time and space; soil variability hampers the interpretation and sampling technique, leading to erroneous data. Gassner et al. (2002) showed that different environmental

factors resulted in the spatial speciation of P. It was possible not only to separate total, soluble and labile P pools, but also, based on the analysis of their spatial continuity, to identify different environmental factors that resulted in the formation of these pools. In these studies, the soluble P fraction was related to the adsorption capacity of the soil, and in particular to the variation in soil texture. Topography and soil erosion were reflected in the distribution of total P, whereas the labile P fraction was influenced by recent fertilizer history.

The premise for the sustainable use of P in agriculture is a balance whereby the P input equals the P output. In conventional arable farming systems, innovative concepts, such as 'precision agriculture' technologies, have the potential to substantially improve the efficiency of nutrient use as the input of fertilizers matches the nutrient demand of the crop. In the past, recommendations consistently aimed at averaging results by arranging replicates across the variability within a field. In contrast, on-farm field experimentation based on soil and plant data will enable the development of site-specific recommendations for fertilizer use, which are more likely to be accepted by farmers.

Intensive livestock farming still is the major source for the non-point nutrient pollution of water bodies and the atmosphere (Isherwood, 1998). Even if the number of animals matches the recommended figure of a maximum of two livestock units per hectare for a sustainable use of the nutrients, the actual application rates are much higher because the wastes are often disposed of on much smaller areas in order to reduce disposal costs. Political decisions rather than scientific solutions are needed to solve this problem effectively.

In the case of P, the fertilizer surplus increases with the level of the P supply of the soil (Schnug, 1996). Applying fertilizer rates higher than the uptake by plants will lead to an accumulation of soluble phosphates in soils, which are a waste of a valuable resource and may become a threat to the quality of water bodies. These examples indicate that the national P balance does not reflect the situation at farm level. National balances obscure the situations on individual farms; the annual nitrogen surplus, for instance, ranges from zero to more than 250 kg per hectare (Schnug et al., 2006b). Based on the national statistics, typical arable farms in Germany already seem to be in a state of nutrient mining as far as P is concerned.

More worrying is the large surplus in the P balance of livestock farms of 21 kg per hectare because of high imports of P with feedstuff and stocking rates that are too high (Schnug et al., 2006b).

A significant change would require a different strategy at the farm, for instance towards organic farming. Organic farms can have much lower stocking densities as the system aims at having closed nutrient cycles. Commitment to sustainability therefore requires a basic restructuring of agricultural production systems. Alternatively, the costs of environmental clean-up might be levied from large conventional farms, or legal action might be taken over the whereabouts of animal manures and slurries.

Another aspect, which is unequivocally related to P fertilization, is that of heavy metals on agricultural soils. The heavy metal content of rock phosphates varies greatly in relation to their origin. So far, for organic farming, only the cadmium (Cd) content of rock phosphates is limited across the European Union 90 mg Cd per kg P2O5 (EU directive 76/116/EEC). In contrast, the limit in the German Fertilizer Ordinance is only 50 mg Cd per kgP2O5. But rock phosphates can also be contaminated with significant amounts of uranium (U), a highly toxic heavy metal that exhibits radioactivity. The U content depends on the origin of the phosphate rock: in general, products of sedimentary origin contain higher amounts than those of magmatic provenance (Kratz and Schnug, 2006). The mean U content of phosphate rocks from different deposits and in selected P fertilizers are summarized in Table 1. The data reveal that U accumulates in the processed P fertilizer, so P fertilization is an important pathway for U building up in agricultural soils. Other relevant contaminants include the rare earth elements and boron. In comparison, the uranium content of farmyard manure and slurry is low, usually less than 1.5 mg U per kg (Table 1).

Towards sustainable phosphorus management

Closing phosphorus cycles

The processing, use and recycling of plant nutrients from industrial processes are essential elements of strategies for waste avoidance. Using agriculture to dispose of wastes may conflict with environmental interests

Table 1 Uranium Content (mg U per kg) of Rock Phosphates of Different Origin and Mineral Phosphate Fertilizer Products. Data from Kratz and Schnug (2006) and Schnug et al. (2006b).

Rock phosphate deposit (country)	Origin (*S, Sedimentary; I, Igneous*)	Range of variation	
		min.	max.
United States	S	65	141
Morocco; Western Sahara	S	75	130
China	S	23	31
Russia	I	27	85
Tunisia	S	32	48
Jordan	S	46	129
Brazil	I	182	220
Israel	S	99	150
Syria	S	75	106
P fertilizer (non-EU)	**Mean**	**min.**	**max.**
P fertilizer	149	8.7	362
Superphosphate	134	80	325
Triple superphosphate	225	186	362
Soft rock phosphate	43	8.7	144
Organic fertilizer			
Cattle slurry	1.4	0.1	3.5
Broiler manure	0.97	0.33	5.0

and can only be a practical option if the legal demands for protecting consumers, soil and water sources are fully satisfied.

It is estimated that about one third of imported P could be replaced by recycled P in Germany. The P excretion of one human adds up to 500 g P per year, and about 58% of sewage sludge is recycled in Germany (Statistisches Bundesamt, 2003). Another approach for retrieving P is its precipitation in urine after separation from wastewater as struvite (magnesium ammonium phosphate). The heavy metal content of struvite can be reduced efficiently to a level below that of manure (Ronteltap et al., 2007). The main problem of sewage sludge and struvite, however, is the risk of contamination with organic xenobiotics (chemicals that would not normally be expected to be present). It has not been possible to produce struvite that is completely exempt from organic compounds (Ronteltap

et al., 2007). Recently developed technologies for the thermochemical treatment of sewage sludges deliver a secondary raw fertilizer material that is comparable in its P efficiency with partly decomposed mineral P fertilizer products but is free from organic contaminants and has a heavy metal content that meets the legal demands for mineral fertilizers (Adam et al., 2008).

Phosphorus and nuclear energy

Uranium is often found with phosphate rock, particularly that of sedimentary origin. It is also an indispensable raw material for producing nuclear power. The unconventional world U reserves in P deposits are estimated to add up to 22 × 106 tonnes and could deliver U for another 440 years for the same price as conventional U resources, which is about five times longer than the timespan calculated for conventional U reserves (see Hu et al., 2009). About 6% of the world's known P deposits exhibit recoverable concentrations of U (Orris and Chernoff, 2002). The technology to extract U from rock phosphates has long been available and was used until the 1990s in Belgium and the United States (International Atomic Energy Agency, 2001). After 1980, the price of U was less than the margin of US$80 per kg U for the profitable extraction of U from rock phosphates. The International Atomic Energy Agency speculated that extraction of U from phosphates in the future depends on either changes in the global market price for U or environmental regulations.

Rock phosphates and processed P fertilizers are one of the main sources of U contamination and accumulation in agricultural soils, and thereby increase U losses to water bodies. Fertilizers with low U content are essential to avoid U accumulation in the soil of intensive agricultural production systems. So extracting U from rock phosphates would serve two purposes: providing U for the nuclear industry, and minimizing the U contamination of agricultural soils and water bodies by P fertilization. But combining an efficient measure of environmental protection with the supply of U for nuclear power is a delicate balance and a tricky concept. Hu et al. (2009) provide a detailed approach for recovering U from rock phosphates for the production of U-235 for nuclear energy and refined P fertilizer products.

Conclusions

It is easy to use the term 'sustainable development' without considering all its implications. We have discussed some substantial conflicts and proposals for solutions with respect to issues of phosphorus fertilization and the concept of sustainable development. However, there is more to sustainable development in agriculture than just production standards. Agriculture shall not only feed the world, but also nourish humanity and encourage an affinity with nature.

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Irrigation for Sustainable Agriculture in Egypt

Abdel-Ghany El-Gindy

Water resources are the critical factor for all agricultural processes and attempts to achieve sustainable development in Egypt. Water management and irrigation technologies are therefore central to all agricultural projects, especially in arid regions. This is particularly important as Egypt is currently trying to improve agricultural production by extending agriculture to desert land, where the problem of water availability is particularly pressing.

The main problems facing attempts to manage irrigation on farms are the inefficient use of water, the cost of irrigation systems, the quality of irrigation equipment, and salinity. There are two main approaches to dealing with these problems. The first approach is integrated water management. The second is to improve the use of water by implementing new irrigation technologies, derived from agricultural research. These can help by saving water, improving soil characteristics, decreasing agricultural drainage, optimizing the use of water, and increasing crop production.

Irrigation and the water shortage

The Egyptian government is making an enormous effort to improve its food production in a bid to prevent food shortages in the future. But the environment is arid and water resources are scarce. The country's total water budget is just 71.2 billion cubic metres per year, and the agricultural sector currently consumes 82% of this. In 1990, Egypt reached the 'water

poverty line' with a per capita share of water of less than 1,000 cubic metres per year, a figure that is expected to fall to less than 500 cubic metres per year by 2030.

The government's policy is to promote modern techniques in the agricultural production system, following an integrated scientific approach that has been verified experimentally and shown to have a positive economic impact. Improved irrigation technologies to save water need to be applied in farms all over the Nile Delta and Nile Valley. The most common irrigation methods used on Egypt's farms are surface irrigation, using gravity, and pressurized irrigation, using sprinklers. The modern designs for surface irrigation systems have proved to be more accurate and efficient, and less expensive, than pressurized systems. But the selection of a suitable irrigation method must take into account a variety of factors, of which cost is just one, alongside efficiency of water use and the ability to provide a uniform distribution of water in the root zone.

Research topics

Agricultural research is clearly an important precursor to the implementation of a strategy for sustainable agricultural development. The government is therefore planning to establish a committee responsible for preparing a comprehensive database that includes all the research findings related to water management and soil conservation practices on farms. In addition, there will also be monitoring and evaluation teams, given the wealth of information obtained from studies aimed at improving water-related technologies and maximizing crop production. For example, researchers have found that precision land levelling (PLL) using lasers have increased the efficiency of water use on some field crops, and shown that the highest sugarcane yield and quality were obtained when using a subsurface drip system rather than any other form of irrigation. They have also explored the effects of different irrigation systems on the amount of water used for a variety of other crops.

National projects and programs

Land reclamation projects

The project to develop the Sinai region covers a total area of 260,000 hectares, and uses a 1:1 mixture of water from El-Salam and sewage water. Its annual water requirements are ark milliard cubic metres.

The project to develop the south of the Nile Valley has three main parts. The first part covers an area of 210,000 hectares, including valleys connected with the Nile in Quena and Aswan, which are directly irrigated by Nile water. The second part involves the Shark El-Owinat, Darb El Arbien and Oasis projects, where 210,000 hectares are irrigated by groundwater. The third part is the Toshka project, where 227,000 hectares are irrigated by pumping water from Nasr Lake.

On-Farm irrigation development

The main goal of this program is to improve the on-farm irrigation systems and rehabilitate the infrastructure in an area of more than 2 million hectares with the aim of rationalizing the use of water in agriculture. By 2017, Egypt's water resources are expected to have increased by 13.5 billion cubic metres thanks to a saving of 10 billion cubic metres from the program to develop irrigation on old farmland, a further 1 billion cubic metres from reducing mismanagement in new farmland, and a saving of 2.5 billion cubic metres from replacing large areas of rice with corn.

The program was developed because Egypt faced a variety of problems: the low efficiency of traditional surface irrigation systems; the continuous reduction in water resources per capita as the population increased; the degradation of soil and water resources as a result of excessive irrigation; the need to grow crops to make the best use of water; the need to increase public awareness of the importance of rationalizing water use in agriculture; the poor distribution of water in old farmland; the poor use of energy for both irrigation and drainage; and the growing environmental pressures in term of natural resources and climate change.

The project is expected to have many additional benefits too: work opportunities for 10–15 million people; energy savings; improving soil fertility and land productivity; an increased rate of agricultural intensification and the modernization of agriculture in the Nile Valley; and

improved human health. The program will: renovate mesqas and marwas by cement lining or the laying of pipes; improve the distribution of water in fields, by using controlling valves; introduce improved surface irrigation systems, by providing gated pipes, laser levelling and new practices for on-farm irrigation management and applying localized irrigation in fruit and vegetable fields; and prepare an agro-ecological zoning map to identify the best land use pattern.

Recommendations

- A complete database including as much information as possible about irrigated land and the available water resources is essential to establish a strategy for water conservation
- A national program to rationalize the use of water in agriculture should be designed and implemented to increase the productivity per unit of water
- A national agricultural meteorological network should be established and linked to a national effective extension system
- A policy for rationalizing water use should be established to encourage farmers to invest in modern irrigation technologies in old farmland
- The technical specifications and quality control standards for the equipment used in modern irrigation should be established
- Crops that consume less water should be used instead of traditional crops that consume more water. For example, sugarbeet should replace sugarcane
- Modern irrigation techniques should be introduced in old farmland
- Water of marginal quality, such as drainage water and brackish water, should be used in irrigation wherever possible, and water from the Nile can be used to irrigate salt-tolerant crops
- A water-users association should be set up to manage the irrigation system and take responsibility for the design and implementation of irrigation systems, for improvements needed to increase the efficiency of water use, and for the equitable distribution of water among farmers who share the same canal
- Courses on the management of natural resources should be developed and taught at schools and universities

The problems facing Egyptian agriculture are severe, but a combination of these actions could help to improve the efficiency of water use on farms. This would reduce the water shortage facing the country in the decades to come, and provide a solid basis for the development of sustainable agriculture in Egypt.

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INNOVATIVE PRESCRIPTIONS IN HEALTHCARE

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New Drugs to Fight Malaria

E. Jane Morris, Zoleka Ngcete, Lyn-Marie Birkholtz and Abraham I. Louw

The global impact of malaria is enormous. The World Health Organization's *2005 Malaria Report* (WHO, 2005) estimated that 3.2 billion people in 107 countries are at risk of contracting malaria. Between 300 million and 500 million new malaria infections occur every year, and the disease causes 2 million to 3 million deaths annually. It has been suggested that there are as many as 660 million clinical cases of malaria each year (Snow et al., 2005).

In Africa alone, each year at least 1 million people die from malaria and there are more than 200 million clinical cases. The impact is greatest for pregnant women and children, and in Africa a child dies of malaria every 30 seconds. Current evidence suggests that the disease can impair intellectual development, with cerebral malaria potentially resulting in permanent developmental abnormalities. Few countries in sub-Saharan Africa report the number of malaria cases each year, so the figures recorded by the WHO probably represent only a fraction of the actual burden of disease. Each year, 57% of new cases occur in Africa, with 30% in Asia and 5% in the Americas. More than 90% of deaths from malaria occur in Africa. The disease also has a severe economic impact on affected communities, with an estimated cost of US$12 billion per year and a consequent decrease in the gross national product.

The United Nations Millennium Development Goal number 6, to 'combat HIV/AIDS, Malaria and Other Diseases', set a target of halting and beginning to reverse the incidence of malaria by 2015. The 2008 progress report points out that there has been less progress in the treatment of malaria than in its prevention (United Nations, 2008). The increasing level

of resistance to front-line drugs has led to a shift in treatment strategy towards artemisinin-based combination therapies (ACTs), which cost more than most of the older, freely available drugs. Artemisinin is the only drug that is currently effective in all regions where malaria is endemic, and progress to develop a new generation of drugs has been slow.

Africa is the continent most affected by malaria, but so far African scientists have had little direct involvement in the development of new drugs, vaccines and diagnostics. The South African Malaria Initiative (SAMI) was created as a research network to increase the involvement of African scientists in developing the means to combat malaria. SAMI programs focus on the discovery of new drugs and drug targets, on the development of improved diagnostic methods, and on understanding the interaction between the Plasmodium parasite and its host, the Anopheles mosquito.

SAMI researchers use cutting-edge biological and chemical techniques to identify drug targets and discover new drugs. It is widely anticipated that the application of advanced molecular-biological technologies would significantly enhance the identification and characterization of new parasitic targets for chemotherapeutic intervention. Here we will outline some of the activities of SAMI researchers in the application of functional genomics and the development of heterologous expression systems in drug discovery.

Functional genomics in drug discovery

Functional genomics encompasses the global analysis of an organism's transcriptome, proteome, metabolome or interactome—the sum of all its messenger RNA 'transcript' molecules, expressed proteins, metabolites or molecular interactions at a particular time. The application of functional genomics in drug discovery is rapidly gaining momentum as a means of determining the response of an organism to drug challenge. Compendium libraries of an organism's response to different drugs can be established, enabling comparison between the effects of different drugs or drug leads, and providing a way of assessing their merits. It also helps us to understand the mechanisms of drug action and drug resistance, the specification and validation of drug targets, and drug target action (Birkholtz et al., 2008).

Evidence is mounting that malaria parasites exhibit transcription and proteome–wide responses to drug treatments, so functional genomics can provide a global understanding of the mode of action of antimalarial drugs. This includes descriptions of measurable responses in the parasite when its development is blocked, in addition to the normal mechanisms that the parasite uses to control its intra–erythrocytic developmental cycle. However, this understanding has not yet been extended to the parasite's metabolome, and our understanding of the parasite on this functional level is currently limited.

Strategies to Validate Drug Targets

There is a need to develop drugs with novel modes of action to combat the increasing problem of drug resistance. This makes it necessary to identify and validate new drug targets. Drug targets can potentially be validated in two ways:

Genetically—by demonstrating that gene disruption or loss of function of a protein results in a disabled organism.

Chemically—by demonstrating that a compound can selectively inhibit protein function, resulting in cell death.

The genetic approach has limited applicability in Plasmodium, as the parasite is not very amenable to classical genetic manipulation, making it difficult or impossible to demonstrate the effects of gene knockdown or knockout. Moreover, the existence of RNA interference machinery in Plasmodium has not been demonstrated.

The chemical approach has been more successful as SAMI researchers have used it to validate drug targets *Plasmodium falciparum*, the most virulent of the four Plasmodium species to infect humans. The polyamine metabolism pathway in Plasmodium has a unique bifunctional S-adenosylmethionine decarboxylase/ornithine decarboxylase enzyme (AdoMetDC/ODC), which shows potential as a drug target. Transcriptome and proteome analysis of polyamine-depleted *P. falciparum* after treatment with known inhibitors of the AdoMetDC/ODC enzyme, in comparison with untreated parasites, has been proposed as a mechanism to demonstrate the scope of the resulting metabolic perturbations (Van Brummelen et al., manuscript

accepted; Birkholtz et al., 2008a). Selective inhibition of ODC alone resulted in decreased production of putrescine, the product of the ODC enzyme, but compensatory pathways appeared to be available to overcome the polyamine depletion (Clark et al., 2008). In contrast, co–inhibition of AdoMetDC/ODC resulted in cytostasis and general transcriptional arrest (Van Brummelen et al., manuscript accepted), confirming that this bifunctional enzyme is a valid drug target.

Drug Target Validation

The identification and validation of drug targets must be based on the biology of the malaria parasite. However, our understanding of Plasmodium biology is currently limited. Although several Plasmodium genomes have been sequenced, almost 60% of hypothetical proteins in the parasite genome have not been annotated, and there are fewer than 200 protein structures in the Protein Data Bank (Birkholtz et al., 2006).

The dearth of protein structure and function information, largely stems from a lack of sufficient protein for detailed structural and biochemical studies. Moreover, the design of protein inhibitors, and the evaluation of their potential as drug leads, requires the ability to study their interaction with a protein target. This in turn requires a source of soluble functional proteins.

To obtain sufficient quantities of protein, it is generally necessary to express the protein in a heterologous host. The challenges to heterologous expression have been examined in a recent review by SAMI researchers (Birkholtz et al., 2008b). Many proteins fail to express in the bacteria *Escherichia coli* for a variety of reasons including high protein disorder, codon mismatch, protein toxicity, unusually basic pI and high molecular weight. SAMI researchers are now exploring a variety of alternative host organisms, including yeasts, baculovirus–infected insect cells and plants.

One mechanism to improve expression and enhance correct folding is codon harmonization, which involves the modification of low–usage–frequency codons to make the translational machinery pause at the correct sites. The coexpression of molecular chaperones from Plasmodium with the protein of interest also shows potential to enhance protein folding.

From drug target to drug lead

Once a drug target has been validated and its structure determined, the next challenge is to identify potential drug leads that will dock with the target. Leads or fragments may be designed and docked with the target in silico, before proceeding to synthesis and testing in the laboratory. Potential leads should preferably meet the requirements of Lipinski's 'Rule of Five' (Lipinski et al., 1997), and it should also demonstrate a lack of toxicity to the host.

The World-Wide In Silico Docking on Malaria (WISDOM) project has taken the in silico approach further. SAMI researchers are collaborating with french scientists in this project, which involves high-throughput screening of large compound libraries against an identified malaria target (Birkholtz et al., 2006).

The road to finding a pre-clinical candidate, and later into clinical trials, involves further testing and may require the involvement of medicinal chemists to modify and improve its activity. The biological activity must be checked at each stage, and again there will be a requirement for functional genomics and heterologously expressed protein.

Conclusions

The road from promise to practice in the development of new malaria drugs is long, complex and expensive. Nevertheless, it is essential that scientists in the developing world, where malaria has the greatest impact, should form an active part of the process. Too often, scientists in malaria-endemic countries are involved only in the last stages of the process when clinical trials are envisaged.

With the advent of modern gene technologies, more tools and techniques are becoming available to speed up the drug discovery process. However, the equipment and infrastructure required to put these techniques into practice are frequently not available in developing countries. African countries in particular need help to develop both the skills and the infrastructure to become actively involved. The mindset that science can do for Africa, rather than with Africa, is outmoded. Partnerships are needed for building

the capacity to enable Africa to solve its own problems. This 'Science With Africa' is very much in the spirit of the conference organized by the UN Economic Commission for Africa and the African Union in March 2008. The development of capacity under the banner of the South African Malaria Initiative represents one small step on this journey.

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Genetic Testing: Delivery, Care and Support

Alastair Kent

The Genetic Interest Group is a registered charity (not-for-profit organization) in the United Kingdom. It is an alliance of about 140 patient support organizations representing individuals and families affected by all forms of genetic disorder, ranging from rare conditions arising from a mutation in a known single gene, to complex common conditions resulting from the interplay of genetic, environmental and lifestyle factors, many of which are not yet fully understood.

Nearly all of the diseases and disorders that affect these individuals and families are intractable, incurable chronic diseases. Many result in progressive disability and premature death. The people affected are therefore dependent on high-quality biomedical research and the availability of the resulting products and services. For this reason, the Genetic Interest Group supports efforts to promote research and development. It is also committed to working to ensure that services, support and interventions to prevent, treat or cure life-limiting genetic diseases are provided in an equitable manner, according to clinical need and the potential to benefit.

The Genetic Interest Group does not itself undertake medical research or provide direct clinical services to patients and families. Rather, it works by strategic advocacy and campaigning to bring a patient and family perspective into the R&D agenda and into the planning and delivery of health care by public- and private-sector providers. It draws its legitimacy from its membership, with whom it is in constant contact to ensure that the views and values it puts forward resonate with the needs and priorities of those affected or at risk.

Progress in opportunities for intervention

In recent years our knowledge of the basic biology of many intractable diseases and disorders has moved forward in leaps and bounds. In the sphere of diagnosis, without which intervention would be all but impossible, we have moved from a reliance on clinical observation and now have a sophisticated range of laboratory tests to support physicians and provide greater precision in diagnostic capability. Advances in microscopy and the development of techniques such as fluorescence in situ hybridization (FISH) allow us to detect small changes in our chromosomes. Biochemical analysis can detect changes in our basic biological pathways, and molecular genetics allows us to sequence our DNA to find slight changes that can have important effects.

There have been similar improvements in the care and support available to those affected or at risk. Increased understanding of the natural history of genetic diseases means that appropriate, comprehensive and comprehensible information, advice and support can be given to patients and families in a timely, user-friendly way. This gives those affected a better opportunity to understand their situation and to take control of their diseases and make informed choices about their care.

Accurate diagnosis also makes it possible to ease the symptoms of genetic diseases, improving the quality of life for those directly affected and easing the situation for their families and carers. And finally, it makes it possible to provide therapies to prevent, treat or cure the condition where these exist. A misdiagnosis or a missed diagnosis represents lost opportunities, resulting in potentially avoidable harm and unnecessary suffering.

As science advances, it is becoming possible to consider strategies that will help to prevent, or at least reduce, the incidence of genetic diseases and disorders.

In terms of public health, fortifying basic foodstuffs with supplements can have a significant effect on the incidence of certain genetic diseases. The addition of folic acid to flour has helped reduce the prevalence of neural-tube defects in many parts of the world, for example, and the addition of iodine to salt has had a similar impact on certain types of mental retardation.

Health-promotion activities can target information at women and couples in a format they can understand and at a time when they are likely to be able to respond. For example, targeted campaigns about the risks of excess alcohol in pregnancy have helped address the causes of Fetal Alcohol Syndrome, reducing the number of babies affected by this condition.

Population screening is increasingly available as a tool for targeting intervention where it can significantly reduce the impact of an otherwise disabling condition. Increasing technology and the falling cost of screening make it easier to test identified 'at risk' populations, such as new-born babies or women aged 35–60, for a growing number of conditions, and to introduce timely preventative or therapeutic interventions where needed.

Finally, the growing number of conditions that can be detected antenatally means that, in societies and cultures where this is a legal option, it is possible to give women and couples much greater control over their reproductive choices. This gives them the option of terminating a pregnancy when the fetus is found to have a significant genetic disease.

Necessity or possibility

Of course, the mere fact of being able to do something does not mean it is right to do it. Rapid technological progress now allows healthcare planners to contemplate a range of possibilities that, if they were all implemented, would far outstrip the ability of even the wealthiest healthcare systems to fund them. Difficult choices still have to be made. Indeed, as the number of possibilities grows, the need for a rational, robust and transparent framework for planning and implementing the delivery of appropriate services becomes ever more urgent.

Such a framework enables healthcare planners and providers to distinguish things that must be done from those that should, and ultimately from those that could be done when everything in the first two categories has already been provided at the necessary level. Prioritization not only ensures the best use of available resources, but also allows for engagement with patients and the broader public in ways that help maintain public confidence in the healthcare system.

There is no 'one size fits all' model here. What works in wealthy nations cannot be applied to middle or low-income countries. Each healthcare system must develop its own framework, taking account of local circumstances, available resources, political constraints, and moral and ethical sensitivities. Whatever shape the process takes, it needs a plan that works, and systems must be in place to monitor its delivery to ensure that patients' needs are being met.

Integrated service delivery

Most genetic diseases, whether they result from the working of one gene or many, are complex. They affect many different bodily systems and their impact changes over the lifetime of the patient. Providing care and support requires help from a range of different clinical professionals, and may also involve people from the fields of education and social welfare.

Making these different activities work together well to secure the best possible outcome for patients and their families, requires good communication between them. It is also essential that the patient and his/her family are seen as a partner in this process, not merely a recipient of the care and support provided—an empty vessel waiting gratefully to be filled from the expertise and the largesse of the professionals involved. Different diseases create different needs, and although the opportunities for intervention are dependent on the resources available, the need for planning is always there. Arguably, planning is even more important in poor countries than in rich ones, as there is little slack in the system, creating an imperative to make the best use of what limited resources are available.

The elements of a plan are shown in Figure 1. The patients and families require a network of logical, timely intervention and for everyone to act together to secure, if not the best possible outcome, then certainly the 'least worst'. After all, many genetic diseases are still incurable, and there needs to be a way of balancing the patient's and the family's needs with clinical, social and economic factors.

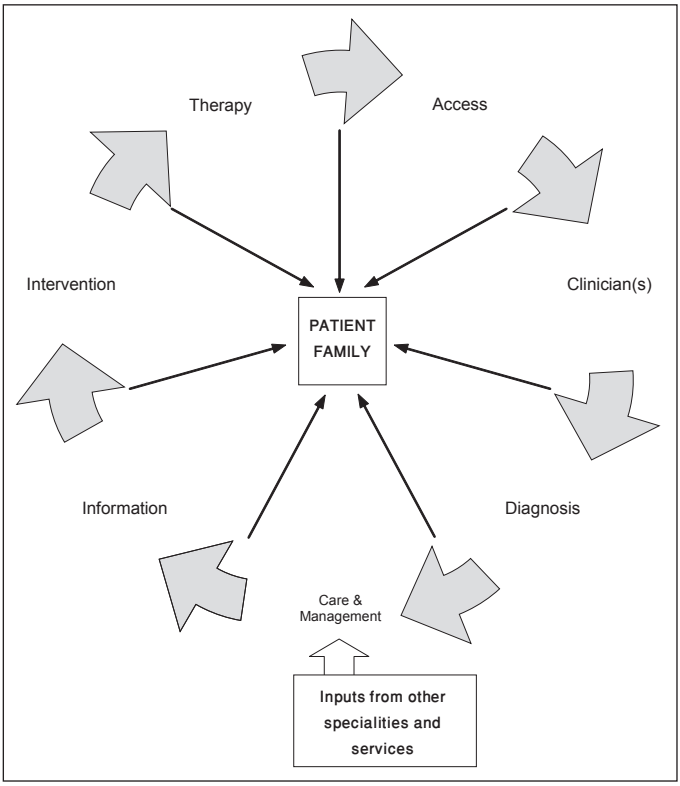

Figure 1 Elements of an Integrated Service Plan.

Critical Success Factors

Access

Nothing can be done if the patient and family affected by a life-limiting disease are unable to get access to health care. There are at least four key factors that determine whether or not a patient can get to the starting line with regard to accessing appropriate health care. They apply in all healthcare systems across the globe.

The first is the overall level of resources devoted to the provision of publicly funded healthcare by the government. This sets the baseline that a citizen can expect to receive in the event of sickness and disease. At best it may extend to comprehensive healthcare provision; at worst it may provide only a rudimentary safety net.

Second, for those fortunate enough to be able to access private health care or to use additional voluntary insurance cover, it may be possible to supplement or replace state provision with services created to respond to individual needs. In many parts of the world, the patient must travel to centers where the relevant expertise can be found, and this will always be a minority option. Most will need to rely on the support of their publicly funded healthcare system.

Irrespective of the wealth or otherwise of the patient, the third factor determining access is the knowledge and understanding of the physician, who is often in the position of the gatekeeper to further progress. If the physician is unable to make an accurate diagnosis (for whatever reason) then future avenues are closed off because the patient does not know where to go for help.

Finally, even if a diagnosis can be made in a timely manner, progress will be limited unless there are plans, referral pathways, guidance and support. Patients need their medical advisers to say: 'I know what this is, I know what to do about it, and I know how to engage with the people who can do it.' Defined referral pathways and protocols are an essential adjunct to clinical judgement in bringing this about.

Diagnosis

Assuming that the patients and families have the access to health care they need, they also need an accurate diagnosis delivered in a timely way. Choury et al. (2000) developed the 'ACCE framework' to determine whether diagnostic tests are fit for purpose in planning patient care. This framework uses four broad criteria as an aid to decision-making by service planners:

- Accuracy
- Clinical utility
- Clinical effectiveness
- Ethical legal and social aspects

These are important considerations, and can certainly be used to evaluate diagnostic assays, but for many patients and families they do not provide a complete answer to the issue of accessing a diagnosis and opening up the resulting possibilities. That requires a 'patient-centered ACCE framework' with the following parameters:

- Availability—can I get it?
- Comprehensible—will I be able to understand and use the results?
- Compassionate—will people care and help me take the necessary action?
- Equity—will I get fair treatment even if my condition is difficult to diagnose and expensive to treat?

Planning to meet patients' needs

Planning frameworks are dependent on two domains of action coming together in a logical, integrated manner. A framework will remain an empty document if mechanisms are not in place to generate the knowledge needed to make the plan, and if there are no steps that have to be taken to ensure that plans are translated into action through systematic implementation procedures backed up by monitoring and evaluation.

Generating knowledge requires attention to several different dimensions if the action is to be robustly underpinned. These dimensions are:

- Research—do we understand the condition and its effects on patients and families?
- Epidemiology—how many people are affected and in what way?
- Possibility—what can be done about the condition and what options do we have?
- Awareness—do specific interventions need to be deployed rather than generalized, nonspecific care?
- Skills—do the clinical professionals have the skills to do this?
- Training—if not, what needs to be done to make these interventions possible?

This 'REPAST' framework, if properly developed, will underpin an implementation strategy that will meet patients' needs and sustain public confidence in the public health system.

Implementation must not be left to chance or to professional goodwill if planners and the public are to be confident that resources will be used to maximise health benefits. Several criteria must be met if the effective implementation of knowledge-based strategies is to be a realistic goal:

- Transparent—can people see how decisions are reached, and who is making them?
- Rational—is decision-making based on robust evidence being examined and interpreted logically?

- Appropriate—does the framework reflect and respect economic, cultural and societal realities?
- Fair—are plans based on needs rather than non-medical factors, such as geography or personal contacts?
- Flexible—as possibilities open up, do plans change accordingly in a timely manner?
- Integrated—do difficult elements of the healthcare system work well with other systems, such as education and social welfare?
- Culturally sensitive—does the provision of health care incorporate religious and cultural sensitivities and respect diversity and minority views?

Adopting the 'TRAFFIC' framework should secure the efficient and effective implementation of evidence-based plans to produce the optimum health benefit per unit of resource. It will also help ensure that patients and their families are at the heart of the planning process, and that planners are answerable to citizens in a fair, challengeable way for the decisions they make.

Cost of clinical effectiveness

Considerations of cost and clinical effectiveness are an inescapable element of healthcare planning. One can argue for a greater proportion of national resources to be devoted to health care, but once the budget is set for a given period then difficult decisions have to be made about provision and reimbursement.

The logic of cost and clinical effectiveness is inescapable. Planners and clinicians need robust systems for deciding:

- What works?
- Who does it work for?
- Under what circumstances does it work?
- How many people need it?
- How much does each person need?
- What will it cost?
- Can we deliver it?
- Do we want it, and is it worth it?

Questions about cost and clinical effectiveness may be largely self-evident, but the methods developed for answering them are often crude, failing to take account of patients' and families' perspectives, and leaving

out important areas of knowledge and experience. Too often they seem to focus on aspects of an intervention that can be measured in a relatively uncomplicated way, rather than on what is most important. Some nations are beginning to incorporate social value criteria into decision-making, but this is far from universal.

Taken alongside the existing methods for health technology assessment, the introduction of the REPAST and TRAFFIC frameworks would go some way towards ensuring that a patient-centerd healthcare planning and delivery system is put in place. It would also provide a brake to the technological imperative that pushes us towards uncritically adopting the latest development. Just because something can be done that does not mean it should be done. REPAST and TRAFFIC are tools that enable all stakeholders to come together to answer the following questions about an intervention or a programme of care:

- Does it do what it says on the tin?
- Is what is says on the tin useful?
- Do we know what to do with it?
- Are we prepared to spend money on it?

These tools work in all contexts and cultures because they can take account of resource-related considerations. They can be applied to both public- and private-sector healthcare systems. They relate to collective and to individual decision-making by professionals and by individuals or families. And they are future-proof, and can be revisited in the light of changing needs and circumstances.

Conclusions

As medical knowledge advances, more and more diseases and disorders will become potentially treatable and curable. Such progress is welcome and offers a beacon of hope to the millions of people and families around the world who are currently living with the daily impact of life-limiting, chronic ill health.

Realizing the potential of genetic medicine will require systematic planning to secure the prompt, equitable application of new possibilities for the benefit of those who need them. The systems developed to secure

the translation of research outcomes into the delivery of clinical services are in their infancy. Ensuring continued confidence in the ability of national healthcare systems to meet the legitimate claims of all citizens as we enter the era of genetic and genomic medicine will require a sustained effort in which all stakeholders, including patients and families, are seen as partners with a valuable and essential contribution to make.

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Molecular Mechanisms of Tumour Complement Resistance and Strategies for Therapeutic Interventions

Wenhan Li and Michael Kirschfink

As part of the innate immune system, complement represents one of the key effector mechanisms of antibody-mediated immunity. Its main roles are providing defence against bacterial infection, bridging innate and adaptive immunity, and disposing of immune complexes and products of inflammatory injury (Walport, 2001a,b). Complement comprises a group of more than 30 proteins that participate in a cascade-like activation process, serve as control proteins, or act as cellular receptors. The complement cascade can be activated by three distinct pathways—the classical, the alternative and the lectin pathway—that all lead to the activation of C3, the central component of the system. Each of the activation pathways leads to the formation of complement's terminal membrane attack complex (MAC), C5b-9. This in turn leads to either cell destruction or, in smaller doses, to cell activation. A balanced action of soluble regulatory proteins (C1 inhibitor, C4b binding protein, factors H and I, clusterin and vitronectin) and membrane-bound regulatory proteins (CD35, CD46, CD55 and CD59) restricts the action of complement at critical stages of the cascade reaction.

Complement is known to provide a rapid and efficient means of protecting the host from invasive microorganisms, but its role in the anticancer immune response remains obscure, and has even been called into question. In cancer patients, endogenous complement activation has been demonstrated with the subsequent deposition of complement components on tumour tissue (Lucas et al., 1996), and neoplastic transformation may be accompanied by an increased capacity of the cells to activate complement (McConnell et al., 1978).

In recent years, antibodies have been designed to direct and concentrate cytotoxicity to the tumour cell (Stern and Herrmann, 2005). This era of targeted therapy has brought to the clinic more than a dozen monoclonal antibodies, including Rituxan (rituximab), designed for relapsed or refractory CD20-positive non-Hodgkin B-cell lymphoma (NHL), Herceptin (trastuzumab) for breast tumours that overexpress human epidermal growth factor receptor 2 (HER-2), and Campath (alemtuzumab), which binds to the protein CD52 and is administered to patients suffering from chronic lymphocytic B-cell leukaemia. The clinical and commercial success of such anticancer antibodies has created great interest in antibody-based therapeutics for haematopoietic malignant neoplasm and solid tumours. However, the therapeutic success of many of these antitumour antibodies is limited by the fact that one of the key effector mechanisms, the activation of complement with subsequent opsonisation (binding enhancement to ald phagocytosis) and cytotoxic elimination of the targeted tumour cells, is significantly limited by resistance mechanisms developed by the tumour.

Molecular mechanisms of tumour complement resistance

The resistance of tumour cells to complement-mediated lysis depends on a large variety of factors, which either limit the quantity of complement proteins deposited on the cell surface, reduce the extent of damage inflicted by MAC, trigger repair processes or even eliminate MAC from the cell surface. Most of the resistance mechanisms are probably also used by normal tissues to resist accidental cell damage from bystander attack by autologous complement.

Resistance depends on basal mechanisms that include: the overexpression of membrane-bound complement regulators (Figure 1); soluble complement inhibitors released by tumour cells to the microenvironment, such as C1 inhibitor, factor H and factor H-like protein; the release of nonspecific complement inhibitors; and the expression of complement-cleaving proteases, such as ectoproteases, sialic acid residues and ectoprotein kinases (Jurianz et al., 1999, Jurianz et al., 2001; Donin et al., 2003).

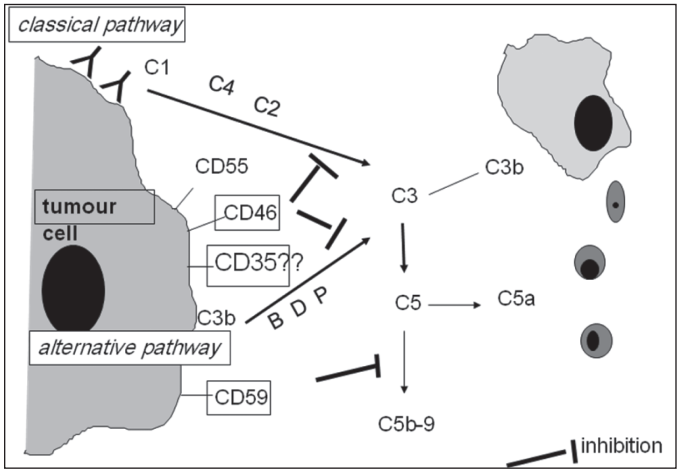

Figure 1 Membrane-bound complement-regulatory proteins, such as CD46, CD55 and CD59, control complement activation on the surface of tumour cells.

Of these, the over expression of one or more surface regulators is considered the most important mechanism of tumour complement resistance and the main obstacle to antibody-dependent tumour immunotherapy. This has been underlined by reports that enhanced expression of membrane regulators is associated with reduced survival in cancer patients (Durrant et al., 2003, Watson et al., 2006). In vivo, the level of expression and cellular location of membrane-bound complement regulatory proteins (mCRPs) in cancer cells may be regulated by various factors (Fishelson et al., 2003). First of all, the variability in expression of mCRPs may be the result of a selective force caused by multiple events of complement attack during neoplastic transformation. Alternatively, the level of expression of each mCRP may reflect a stage in the differentiation of specific tumour cells. Poorly differentiated colorectal carcinoma cells

express low or no CD59, whereas differentiated carcinoma cells express higher CD59 levels (Koretz et al., 1993).

The basal resistance of tumour cells seems to be under the control of various external stimuli, such as cytokines, toxins and hormones, which are released into the microenvironment by neighbouring tumour or stromal cells. For example, TNF-a and the interleukins IL-1j3 and IL-6 have been shown to increase the in vitro expression of CD55 and CD59 but to decrease CD46 expression in hepatoma cells (Spiller et al., 2000). As shown in Figure 2, breast carcinoma cells respond to various cytokines with reduced complement sensitivity, but with different effects on the expression level of mCRP. Anoxic conditions may also affect tumour-complement interaction in situ by reducing CD59 expression. Furthermore, malignant cells may react to low-level complement activation by increasing their level of protection from complement.

Treatment with certain chemotherapeutic agents not only elicits multidrug resistance (MDR) but also complement resistance. This resistance is not conferred by P-glycoprotein, but is at least partly due to the overexpression of mCRPs (Odening et al., 2009).

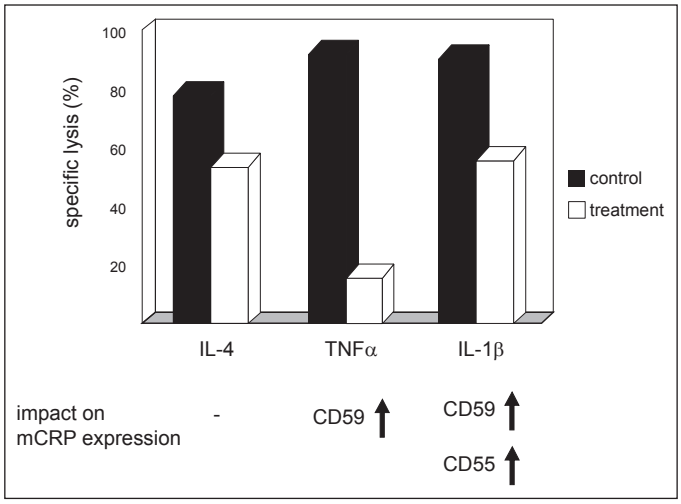

Figure 2 Cytokine-induced resistance to complement-mediated cytotoxicity in T470 breast carcinoma cells. Treatment with the cytokines IL-4, TNF-a and IL-1 b increase the resistance of the tumour cell to complement attack, with different effects on the expression of complement regulators (mCRPs).

Intervention strategies to overcome complement resistance

With a view to sensitizing tumour cells to the patient's complement system, two major strategies have been developed to overcome the protective capacity of surface complement inhibitors: neutralization of mCRPs by blocking antibodies, and knockdown of mCRP expression. Here we will consider each of these in turn.

Antibodies blocking surface complement inhibitors

The activity of mCRPs can be inhibited by monoclonal antibodies directed to CD46, CD55 or CD59, which block their function and increase the susceptibility of tumour cells to complement-mediated lysis. These antibodies are usually poor activators of complement on their own, so they are often used together with complement-fixing antibodies or other complement activators for testing the involvement of specific mCRPs in cell resistance. Neutralizing CD59 with monoclonal antibodies produces efficient sensitization to complement-mediated lysis of various carcinomas in vitro and in vivo, such as neuroblastoma cells, leukaemic cells and breast, ovarian, renal and prostate carcinoma cells. In vivo, antibody targeting of CD55 and CD59 with human neutralizing mini-antibodies to CD55 and CD59 (MB55 and MB59) has been shown to increase the antitumour activity of rituximab in mice (Macor et al., 2007). The combined application of optimal concentrations of neutralizing monoclonal antibodies directed to CD46, CD55 and CD59 has been shown to be effective in breast, ovarian and prostate carcinoma cell lines (Donin et al., 2003).

Selective targeting of mCRP on tumour cells is required because mCRPs are widely expressed on the surface of normal tissues. The construction of bispecific monoclonal antibodies consisting of one F(ab) moiety directed to a tumour-specific antigen and another one directed to an mCRP offered this opportunity. However, to avoid significant binding to normal tissue, the tumour-directed F(ab) moiety needs to be of high affinity (Gelderman et al., 2002a). Bispecific antibodies that recognize tumour antigens and mCRPs, such as CD55 or CD59, induced effective tumour cell death with only marginal effects on bystander cells. Anti-HLA–anti-CD55 bispecific monoclonal antibody, in the presence of normal human serum, increased

C3c deposition on colorectal cells compared with anti-HLA monoclonal antibody either alone or with a mixture of anti-HLA and anti-CD55 monoclonal antibodies (Gelderman et al., 2002b). Anti-Ep-CAM–anti-CD55 bispecific antibody also increased C3 deposition on cervical and colorectal carcinoma cells, as well, or even better than anti-Ep-CAM monoclonal antibody conjugated with CVF or C3b (Gelderman et al., 2002a,b).

Interference with complement regulator expression

Exposing hepatoma cells to INF-y decreases the expression of CD59 and CD46 (Spiller et al., 2000). Similarly, fludarabine downregulates the level of CD55 expression on B lymphoma cells and increases their lysis by rituximab and human complement (Di Gaetano et al., 2001). A more promising approach is the downregulation of complement regulators by antisense or other RNA-silencing strategies. We have shown that mCRP expression on tumour cells can be significantly inhibited by antisense oligonucleotides. Their application for the specific knockdown of CD46 and CD55 abolished the complement resistance of tumour cells of various histological origin (Zell et al., 2007).

Today, small interfering RNA (siRNA) technology represents the most efficient and most widely used antisense strategy (Takeshita & Ochiya, 2006). We have designed potent siRNAs for the efficient downregulation of the mCRPs, CD46, CD55 and CD59. siRNA-dependent mCRP downregulation affected complement resistance, resulting in enhanced lysis of target cells. Substantially smaller amounts of siRNA are required to achieve similar mCRP downregulation compared with antisense oligonucleotides of the same specificity. Miyagishi et al. (2003) showed that the half-maximal inhibitory concentration (IC50) for siRNAs is approximately 100–folds lower than for antisense oligionucleotides. Varela et al. (2008) reduced the expression of Crry (a mouse C3 inhibitor that is similar to the human CD46 regulator) on murine bladder cancer cells by siRNA, resulting in increased susceptibility to monoclonal antitumour antibodies and complement in vitro. Furthermore, siRNA-induced downregulation of Crry in a syngeneic mouse model of metastatic cancer

led to a significant decrease of tumour burden and an increase in the survival of challenged mice. Time-course experiments of siRNA-induced mCRP inhibition show that a single transfection of siRNA already causes long-lasting silencing of target-protein expression. This is in accordance with the observation that siRNA molecules, once successfully transfected, are well protected from nuclease activity (Bertrand et al., 2002).

Knockdown of surface complement regulation and subsequent enhancement of complement sensitivity of the targeted tumour cells could be further improved by the combined application of mCRP-specific siRNAs and antisense oligonucleotides, as demonstrated by Hemmings-Mieszczak et al. (2003). RNAl and DNA-antisense strategies have different molecular mechanisms for post-transcriptional gene silencing, so it is conceivable that a combined or subsequent application of siRNAs and S-ODNs further improves complement-mediated killing of targeted tumours. As recently reported by Donev et al. (2008), another option may be interference with the complement inhibitor genes by targeting regulators of their expression.

Great progress in RNAl therapeutic research has recently been made, taking siRNA technology from research to clinical trials. However, the lack of targeted siRNA delivery remains the major obstacle to its therapeutic application in vivo. Possible devices to enable systemic administration and delivery are based on liposomes (Li & Szoka, 2007) or self-assembling nanoparticles respectively (Algner, 2007). Experiments are being planned to selectively target mCRP-specific siRNAs to tumour tissues and to disseminated metastatic lesions by conjugating targeting ligands (such as monoclonal antibodies) to these carrier devices. When targeted systemic delivery is achieved, complement regulator-specific siRNAs may be used as an adjuvant to improve the therapeutic efficacy of antibody- and complement-based immunotherapy to treat cancer.

Conclusions

Tumour cells use various strategies to escape from immune surveillance and attack, and these restrict the efficacy of anticancer monoclonal antibodies. The main obstacle to antibody-based tumour immunotherapy

is thought to be complement resistance. The main resistance mechanism is based on the surface overexpression of complement regulatory proteins, which target the complement cascade at different steps of activation. The current strategies to overcome this resistance focus on the inhibition of membrane complement regulators, either by blocking antibodies or by targeted knockdown of these inhibitors on tumour cells. These strategies will enhance the efficacy of antibody-based tumour immunotherapy.

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The Molecular Pathway to Personalized Medicine

Sergie D. Varfolomeyev, Vectoria S. Kurova and Kristina Y. Fedorchenko

When the Human Genome Project successfully sequenced the genome of a human, it opened the floodgates to an almost overwhelming amount of scientific data. Much of it has focused on how to interpret the information the human genome contains, and how to use it to provide advances in other areas, notably medicine. In addition, there has been a push to map the genomes of other organisms. At present, the genomes of more than 1,000 microorganisms, plants and animals have already been mapped, and the process is continuing apace.

The interpretation of the human genomic structure has presented opportunities for a wide variety of fields of science, technology and medicine. The International Union of Pure and Applied Chemistry (IUPAC), for example, has launched a project in post-genomic chemistry, seeking to identify the most meaningful trends in molecular research initiated by the Human Genome Project (Varfolomeyev et al., 2005).

One of the most exciting outcomes of genomic research is the opportunity it presents to study the genomes of vast numbers of individuals to reveal the differences between them at the levels of genes and proteins. Modern biochemical methods make it possible to provide a detailed molecular genetic typing of human populations, studying genetic polymorphisms and enzymatic and molecular-receptor processes, for example, in different individuals. As more people have their genetic

profiles mapped, it will be easier to identify individuals from just a trace sample of biological material.

One area that is certain to benefit greatly from genomics is medicine. Post-genomic and proteomic research have already given rise to new fields of medicine, such as cardiogenomics, oncogenomics, neurogenomics and pharmacogenomics. As the predisposition to diseases in many cases has a genetic basis, people are starting to talk of developing individual medicine based on people's individual genetic make-up.

The molecular genetic approach has opened up avenues in the humanities too. The analysis of structural features of genomic DNA passed from generation to generation underlies the idea of ethnicity, leading to the rise of fields such as ethnogenomics and genetic geography.

Just as the influence of genomics will touch many spheres of life, so studies based on human molecular polymorphism will touch many scientific disciplines. It is this interdisciplinary nature that led the Russian Academy of Sciences and the Lomonosov Moscow State University to form, in 2006, a multidisciplinary project based around the diversity of human biomacromolecules (Varfolomeyev, 2007).

Proteomics as a platform for biomedical diagnosis

Of all the avenues opened up by genomics, perhaps the most exciting is the opportunity to tailor medicine to individuals, and this is an area we have pursued as part of the Russian project. Individual medicine requires the identification of human proteins. The most convenient approach is to use biological fluids, which can be obtained by a non-invasive procedure, especially urine, sweat, tears and the condensate of exhaled breath. The proteins can then be identified by mass spectrometry.

Proteomics of exhaled breath condensate

Exhaled breath condensate (EBC) contains the biological markers of lung diseases (Hunt, 2007), along with a wide range of different substances including salts, lipids and proteins (Paredi et al., 2002; Huszar et al., 2002;

Shahid et al., 2002; Scheideler et al., 1993; Wood et al., 2003). The most commonly used condensers are EcoScreen (Erich Jaeger, Hochberg, Germany), RTube (Respiratory Research, Charlottesville, USA) and home-made glass or Teflon devices (Rosias, 2006). Each sample taken represents a breath condensate exhaled for 10 minutes during tidal breathing with a nasal clip. Samples were collected in Teflon tubes at –10°C using an EcoScreen condenser that prevents saliva from being collected.

Using a standard proteomic approach, we identified a range of proteins, including keratins, in the condensates of 17 young, healthy, non-smoking donors. These proteins were then used as a control for comparing the proteomes of healthy people with those of people with respiratory diseases.

Mass spectrometry

Proteins were identified against the human NCBInr protein sequence database, assuming the digestion enzyme trypsin. The score obtained was considered significant if it indicated identity between observed and theoretical peptide sequences. Proteins were accepted as identified if at least one unique peptide was identified with a Mascot probability-based score of more than 70 or if more than two unique tryptic peptides were defined with significant scores.

EBC protein levels

EBCs were collected from 17 subjects for 10 minutes without a protective filter before the air inlet. EBC pH in volunteers averaged 7.12±0.08 without de-aeration, indicating healthy airways (Vaughan et al., 2002), as pH has been shown to be a reliable method for assessing and monitoring airway inflammation. Protein levels were estimated from silver-stained SDS-PAGE. The EBC bands had lower intensities than standards. Taking into account the sensitivity of silver stain, we conclude that each 250 μl sample contains much less than 1 μg protein, so the protein concentration in EBCs is less than 1 μg per ml EBC.

Proteomic analysis of young, healthy, non-smoking donors

Proteomic investigation of the EBCs of 17 healthy, non-smoking donors between 20 and 36 years of age revealed that the major proteins are cell keratins, whose spectrum is polymorphous for different people. Pairs of cytoskeletal keratins 1/10 and 2/9 are invariant for most probes. No mutations in the sequences of these proteins in healthy donors have been detected, but other keratins are substantially different between samples. Keratins 3, 4, 7, 8, 13, 15 and 19 are homologues of keratins 1, 10, 2, 9, 5, 6, 14, 16, 17 and 25 and homological fragments have been identified. Keratins whose characteristic peptides were identified, enabling us to identify these proteins, are 1, 10, 2, 9, 5, 6, 14, 16, 17 and 25. Keratin 9 was the only keratin found in samples from all 17 donors.

Apart from keratins, dermcidin (found in samples from 16 donors), prostaglandin H2 D-isomerase (PGDS2 (6 donors), alpha-1-microglobulin/bikunin precursor (AMBP) (8 donors), ubiquitin (6 donors) and cystatin A (5 donors) were also frequently found. In contrast, some proteins appeared only in samples from just one or two donors: immunoglobulin light chain region (1 donor), human basement membrane heparan sulphate proteoglycan core protein (HSPG2) (2 donors), leukocyte-associated immunoglobulin-like receptor 1 isoform-a precursor (LAIR1) (2 donors), lysosomal membrane glycoprotein-2 (LAMP2) (1 donor), cerebroside sulphate activator (CSA) (1 donor), kininogen 1 (1 donor) and serum albumin (1 donor).

We also condensed and collected air from the room to see whether freely circulating proteins could be interfering with the samples of human exhaled proteins. We found keratins 1, 14, 2 and haemoglobin subunit beta-1, so these cannot be considered as proteins for diagnostics.

Proteomes of Young, Healthy, Non-Smoking Donors

Our investigation has shown that it is necessary to analyse both individual EBCs and mixtures of them to increase the concentration of minor proteins and to obtain exhaustive information about the protein content of EBCs from similar donors. Salt and lipids in the samples can potentially

interfere with the mass spectrometry, but these impurities can be removed by using methanol and chloroform.

Our studies of EBCs from 17 healthy, non-smoking donors between 20 and 36 years of age revealed that the major proteins are cell keratins. However, we failed to discriminate between some keratin homologues, however, such as keratins 13, 15 and 10; 14 and 16; 4, 3 and 6; and 7, 8 and 1. Some were identified by their unique peptides, but others could be neither identified nor excluded. Several of these keratins could be important in diagnosing, classifying and typing lung carcinomas (Moll et al., 2008). Our results lead us to speculate that the respiratory tracts of different people have different levels of expression of various keratins, and it is likely that there is keratin polymorphism in the epithelium. We only identified keratins 5, 6 and 14 known to be expressed in the human airway (Hoffmann et al., 2008). Most of the keratins found in EBCs belong to skin epithelia and hair follicles (Moll et al., 2008), so they were assumed to be exogenous components of EBCs.

We used two approaches to establish the nature of the keratins in EBCs. First, we collected EBCs from donors who used the protective filter described above to separate inhaled air from dust. We compared EBC proteomes obtained with and without the anti-dust filter and found no differences between them. We therefore believe that the exogenous keratins are continuously deposited on the lining of the airway throughout the lifetime, making the keratin content of EBC dependent on both condition and time. In addition, breathing with the filter seemed to be rather difficult, so it is not recommended for patients with laboured breathing or artificial pulmonary ventilation.

The second approach investigated the proteome detected in ambient air. The identification in the air of a number of keratins suggests that they occur in the respiratory tract exogenously and are probably partially retained by the respiratory system. Exhaled proteins can accumulate with dust indoors and be inhaled again, perhaps by other people. Such freely circulating proteins should be excluded from the proteome analysis as they have no diagnostic significance.

We also identified 12 non-keratinic proteins in individual EBCs from healthy, non-smoking people. Of these, dermcidin is a protein antibiotic that originates in the sweat glands, so it is probably also exogenous, but

other proteins frequently found in EBCs from healthy donors could have a diagnostic role. Cystatin A, for example, was characterized initially as an inhibitor of lysosomal cysteine proteases, or cathepsins. Cathepsins are involved in the processing and presentation of antigens, as well as several pathological conditions, such as inflammation and cancer. However, alternative functions of cystatins have recently been proposed: they also induce the synthesis of tumour necrosis factor and interleukin 10, and stimulate the production of nitric oxide (Kopitar-Jerala, 2006).

Prostaglandin H2 D-isomerase, in conjunction with prostaglandin endoperoxide synthase (cyclooxygenase), mediates the formation of prostaglandin D2 from arachidonic acid in mast cells (Tanaka et al., 2000) and Th2 cells (T-helpers) (Matsuoka et al., 2000). Prostaglandin D2 is an allergic and inflammatory mediator that activates two distinct types of receptor and causes the contraction of airway smooth muscle (Hirai et al., 2001; Spik et al., 2005). It also mediates the chemotaxis of eosinophils and basophils into the lungs (Spik et al., 2005). Thus prostaglandin D2 regulates allergic reactions, especially airway inflammation, via two receptors (Urade and Hayaishi, 2000). Prostaglandin H2 D-isomerase participates in allergic and inflammatory reactions (Psaty and Furberg, 2005) and can be a good target for anti-allergic and anti-inflammatory drugs (Kanaoka et al., 2000).

Finally, the alpha-1-microglobulin/bikunin precursor secretes two proteins to the blood. Alpha-1-microglobulin is found in blood and connective tissue in most organs. It is most abundant at interfaces between the cells of the body and the environment, such as the lungs, intestine, kidneys and placenta. Alpha-1-microglobulin inhibits the immunological functions of white blood cells in vitro, and its distribution is consistent with an anti-inflammatory and protective role in vivo (Akerström et al., 2000). The second protein, bikunin, is a Kunitz-type proteinase inhibitor responsible for most of the antitryptic activity of urine, so it is known as the urinary trypsin inhibitor (Mizon et al., 2002). Its excretion increases in inflammatory conditions so it is often considered to be a positive acute-phase protein. However, the gene that encodes bikunin is downregulated in inflammation. In human plasma, the main part of the bikunin molecule is covalently linked to one or two homologous peptide heavy chains, forming high-molecular-weight proteinase inhibitors. Urinary bikunin determination provides information about the severity of systemic

proteolysis occurring in inflammation. It has also been shown that during inflammatory diseases, concentrations of high-molecular-weight bikunin products in the serum are dependent on their increased utilization, as well as on the regulation of their biosynthesis (Mizon et al., 2002).

Conclusions

All these proteins are normal participants of metabolism, and their irregular appearance does necessarily indicate ill health, but changes in their expression levels are related to diseases. This is why we developed the procedure for the rapid analysis of exhaled breath condensates. We optimized the preparation of EBC samples. We compared different methods for concentrating proteins used in previous studies for the proteomic analysis of EBCs. Our results allowed us to choose the most effective procedure when using samples with very low protein concentrations, such as EBCs. Our proteomic analysis of EBCs from healthy, non-smoking donors was therefore quick, effective and suitable for use in clinical diagnostics.

Our results show that the samples obtained featured various different proteins, including keratins. To characterize the composition of the samples more completely, it is necessary to further analyse both mutations in the primary protein sequence and post-translational mutations. This information will underlie the development of methods to diagnose pathologies in humans, such as cancer of lungs, where the markers are products of the molecular polymorphism of keratin genes.

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The Human Immune Response to the Hepatitis B and C Viruses

Farha El-Chenawi

Hepatitis is a disease of the liver, usually caused by one of several hepatitis viruses, although other viruses, drugs and alcohol can cause hepatitis. It can either be acute, lasting less than six months, or chronic, if it lasts longer. The immune response has two primary functions: removing the infection, and limiting damage to the liver.

Many hepatitis viruses cause a cytolytic infection, in which viral replication occurs that damages host cells. This infection provides a clear danger signal that alerts the host's innate and adaptive immune defences to eliminate the virus and terminate the infection. Of the hepatitis viruses, only the hepatitis B (HBV) and hepatitis C (HCV) viruses cause chronic infections, and to do this they must evade the host's immune responses. Understanding the mechanisms used by HBV and HCV to evade host immunity is central to understanding their pathogenicity and is an essential step towards the development of effective therapeutic strategies.

Immune responses

There are two forms of immune responses to viral infection: the innate response, which is a mediated complement, phagocytes and natural killer (NK) cells. The second is the adaptive response, which exhibits the properties of immunological memory, antigen specificity and diversity.

In response to viral attack, antibodies bind viral proteins, including intact viral envelope proteins, leading to the clearance of circulating virus particles. CD4+ T–cells then recognize viral antigens bound to major histocompatibility (MHC) class II antigens on the surface of antigen-presenting cells (APCs). They proliferate and produce cytokines that augment the humoral and cellular immune response to the antigens. CD8+ T–cells recognize antigenic peptides bound to class I MHC molecules, and may be activated to lyse the APCs or produce cytokines

Viral evasion mechanisms

Triggering an inadequate immune response

The virus can avoid inducing a sufficient adaptive immune response by expressing only a low level of antigen or by infecting the host's APCs. This results in Th1 cells releasing inappropriate cytokines and a lack or low frequency of neutralizing antibodies.

Using reverse transcriptase to hide

HBV can encode a reverse transcriptase that enables the virus to integrate its own DNA within the host genome, rendering it invisible to the immune system. HCV on the other hand, which has RNA as its genetic material, does not encode a reverse transcriptase, so it cannot integrate with host DNA.

Loss of antigenicity

Mutation within the precore and core genes of HBV can result in loss of expression of the hepatitis e antigen (HBeAg), effectively removing one of the key targets for the immune response and hiding the virus. No similar mechanism has yet been reported for HCV.

Escape from antibodies

Antibodies directed against the s antigen of hepatitis B (HbsAg) are thought to form complexes with free virus particles, removing them from circulation and possibly preventing their attachment and uptake into susceptible cells. In HCV, clustering of mutations can occur in the

hypervariable region of the E2 envelope gene, which encodes antibody-binding domains. These mutations encode changes in the HCV envelope protein, enabling it to avoid the antibody binding that may block infection or aid clearance.

Interfering with antigen processing and presentation

The endogenous and exogenous antigen-presenting pathways that generate peptides and present them to T–cells are now understood. HBV and HCV have evolved strategies to evade each step in these pathways, including mutations in amino acids flanking the epitopes that influence peptide processing, downregulation of peptide transporter genes, downregulation of MHC expression, and retention of MHC class I proteins in the endoplasmic reticulum, possibly through interference with the transport-associated protein (TAP) transporter.

Evading the T–cell receptor repertoire

A patient expressing human leukocyte antigen (HLA) molecules that are incapable of presenting early or early-to-immediate viral proteins may not be able to mount a response to the first wave of infection. The virus can then escape the immune response and cause a chronic infection. Examples of this phenomenon include the HBV core protein, which contains only a single HLA-A2 epitope, and the HCV core protein, which contains only one HLA-B7 epitope.

The ability of a T–cells to respond to a MHC peptide complex is determined by the specificity of the T–cells receptor (TCR). The TCR repertoire is shaped by the host MHC background and self peptides to ensure that T–cells express TCRs that recognize foreign peptides presented by self MHC but not self peptides or foreign MHC.

The selection of the TCR repertoire results in the deletion of 95% of T–cells during T–cells ontogeny. It is therefore possible that some people will have gaps in the T–cells repertoire that prevent them from recognizing some viral proteins. HLA molecules play an important role in T–cells repertoire selection, so this phenomenon may appear to be associated with specific HLA types.

Interfering with T–cell activation

The efficient activation of T–cells requires the engagement of a variety of ligands and receptor molecules, in addition to the interaction between TCRs on the surface of T–cells and MHC–peptide complexes on APCs. These molecules contribute to both adhesion between T–cells and APCs, and co-stimulation of T–cells. Transient TCR engagement that is not accompanied by a second signal leads to T–cell anergy and immune escape. By interfering with the expression or interaction of these co-stimulatory molecules, hepatitis viruses can potentially evade host immunity.

Disrupting the Function of Activated T–cells

Once T–cells have been stimulated by antigen recognition, they become functionally active. Most CD4+T–cells secrete cytokines that stimulate humoral (Th2) or cellular immune responses (Th1). CD8+ T–cells either exhibit MHC-restricted antigen-specific cytotoxicity or secrete cytokines, or both.

Not all T–cell epitopes are equal, however. Some epitopes, known as immunodominant epitopes, elicit vigorous polyclonal T–cell responses in most infected individuals. Other epitopes are poorly immunogenic, however, and these are known as subdominant epitopes, and a third class, known as cryptic epitopes, may only be revealed by peptide stimulation in vitro. Loss of the immunodominant epitope may be sufficient to establish a persistent, chronic infection. Maximal stimulation by immunodominant epitopes, on the other hand, can result in T–cell exhaustion, whereby T–cells become unresponsive following prolonged stimulation. Prolonged maximal stimulation of immunodominant T–cells can even lead to T–cell death by apoptosis, leaving only T–cells that recognise subdominant epitopes.

Interfering with cytokines

Once the viral infection of host cells is established, the translation and expression of viral proteins can result in the release of molecules that can interfere with host immunity, enabling the virus to evade the immune response. Most viruses induce the expression of host antiviral cytokines, including interleukin (IL)-1, tumor necrosis factor (TNF), IL-8 and interferons (IFNs). The actions of these cytokines on host cells are

mediated by cytokine receptors. Many viruses have evolved analogues or antagonists of human cytokines and their receptors, and these can modulate host immune responses.

HCV immunization

Work is underway to develop a vaccine against HCV, but it faces a series of formidable obstacles. HCV is highly heterogeneous, and a vaccine may need to be multivalent, rather like poliovirus vaccine, if it is to provide protection against multiple serotypes. But encouraging results have been obtained using recombinant envelope proteins (E1 and E2) expressed in mammalian cells as immunogens. These have been shown to induce a short-lived, specific anti-E1 and anti-E2 response in immunized chimpanzees, and have provided a partially protective effect from challenge with small amounts of homologous viruses.

If hepatitis vaccines can be developed successfully and manufactured on a large scale and at a low cost, there is clearly great scope for the large-scale prevention of HCV-induced liver disease on a global scale.

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Nanotechnology in Medicine

Hassan M. E. Azzazy

Nanoparticles have the potential to benefit a range of diagnostic and therapeutic applications. An assortment of nanoparticles has been constructed of different sizes, shapes and composition, and with a variety of chemical and surface properties. Nanoparticles have unique electrical properties that make them excellent semiconductors and imaging agents, and their extremely small size allows them to penetrate cells and interact with cellular molecules and organelles.

Super-paramagnetic iron oxide nanoparticles are useful as contrast agents in magnetic resonance imaging (MRI) and have been used for bioseparations and the targeted delivery of drugs or DNA. Quantum dots are semiconductor nanocrystals that can emit intense and stable light in every colour of the rainbow, depending on their size. Quantum dots of different sizes can be simultaneously excited by a single wavelength far removed from their respective emissions, which enables multiplex diagnostics. Conjugating quantum dots to biological molecules adapts them for target recognition. Colloidal gold nanoparticles exhibit surface-plasmon resonance-enhanced optical properties and can also be conjugated to biomolecules, providing possibilities for tissue targeting and imaging. They can also be used to destroy tissues by local heating or to release a payload of therapeutic drugs because electrons of the gold resonate in response to incoming radiation, causing them to both absorb and scatter light. Finally, biodegradable nanoparticles made from different polymers have been assessed for sustained and targeted drug delivery.

More work is necessary to assess the toxicity of nanoparticles and fully optimize their use for medical applications. Here I will review the

properties and advantages of several nanoparticles. I will consider how nanoparticles can be used to develop diagnostic assays and smart drug delivery systems, and discussion the regulatory framework for their use.

Introduction

The pursuit of methods for the detection of increasingly small amounts of biomolecules can be traced back to the mid–1970s. However, most of the advances and research in the field of nanotechnology, particularly in the development of nanoparticles, have been made in the past decade (see, for example, Salata, 2004; West and Halas, 2003; Weiss, 1999). Nanoparticles are tiny, typically about 1–100 nm (Liu, 2006), which gives them physical and chemical properties that are very different from those of the same material in bulk form. Nanoparticles are also structurally robust and their physical properties can be tailored by altering the particle size, shape and composition. Being about the size of a typical biomolecule or cellular organelle allows them to have a nearly one-on-one interaction with the biomolecule of interest (Azzazzy et al., 2006; Azzazzy et al., 2007; Jain, 2005). Several types of nanoparticle have been developed, including quantum dots, magnetic nanoparticles, dendrimers, silica nanoparticles, gold nanoparticles and biodegradable nanoparticles, such as phospholipid nanosomes. The properties of nanoparticles make them promising for use in various medical applications including in vitro diagnostics, where they promise increased sensitivity, speed and cost-effectiveness, and drug delivery, along with several of other therapeutic applications. The three most promising nanoparticles, which I will discuss here, are quantum dots, gold nanoparticles and super-paramagnetic nanoparticles.

Quantum dots

Quantum dots are inorganic fluorophores with a typical diameter of two to ten nm. A quantum dot consists of a core semiconductor covered with another shell semiconductor that has a larger spectral bandgap. The shell serves to increase the quantum dot's quantum yield as well as its

photostability. Quantum dots have broad-range excitation, strong narrow emission bands, and high photostability; their emission properties can be controlled by varying their size and composition (Azzazzy et al., 2007; Fortina et al., 2005; Michalet et al., 2005). Their emission wavelengths can range from about 400 nm to 2,500 nm (Cuenca et al., 2006). The fluorescent signal generated by quantum dots can be detected using different techniques including fluorescence microscopy and fluorometry (Michalet et al., 2005).

Although quantum dots are typically insoluble in water, they can be made biocompatible by several strategies including silanization and coating with a polymer shell, allowing them to be used in biological systems. In addition, they can be adapted to recognize specific targets by conjugating them to a variety of biomolecules, such as antibodies, peptides, streptavidin and oligonucleotides (Azzazzy et al., 2007; Michalet et al., 2005).

Applications

Quantum dots are particularly suitable for immunolabelling applications, cell motility assays, in situ hybridization, and as live cell markers (Alivisatos et al 2005; Bruchez, 2005). They can also be used as nonspecific fluorescent dyes (Michalet et al., 2005; Alivisatos et al 2005).

Diagnostic and imaging applications

Agrawal et al. (2006) developed a homogenous real-time immunoassay using antibodies conjugated to different quantum dots. The assay has a detection limit of ten target molecules (genes, intact viruses or proteins) and does not require target derivatization. Tripp (2007) subsequently used functionalized nanoparticles conjugated to monoclonal antibodies to rapidly and specifically detect respiratory syncytial virus in vitro and in vivo.

Quantum dots can be used to image cellular organelles, as demonstrated by Biju et al. (2007), who conjugated quantum dots to the insect neuropeptide allostatin, which has high cellular delivery efficiency. This allowed imaging of the cytoplasm, microtubules and nucleus, where the allostatin was localized. Also, Wu et al. (2003) developed an assay for the detection of the receptor Her2 (hairy-related-2 protein) on SK-BR-3 breast-cancer cells. The assay used humanized anti-Her2 antibody and a

biotinylated goat anti-human IgG secondary antibody. Her2 was detected by streptavidin-coated quantum dots. In another imaging application, quantum dots were used to map sentinel lymph nodes at a tissue depth of 1 cm using oligomeric phosphine-coated quantum dots that emit in the near-infrared region, and this may be used for surgical guidance (Kim et al., 2004).

Therapeutic applications

The work of Lai et al. (2003) exemplified the use of quantum dots in controlled drug release. They used surface-modified CdS quantum dots as chemically removable caps to retain drug molecules and neurotransmitters inside a mesoporous silica nanosphere-based system. The CdS quantum dots ensure that the drug is inside the system and prevent it from leaking outside the spheres prematurely until it is released by disulphide bond reducing reagents.

Quantum dots can also be used in photodynamic therapy, which is based on the localized generation of cytotoxic singlet oxygen (the lowest excited state of the oxygen molecule in which all the electron spins are paired; it is very reactive and has a lifetime in solution in the microsecond range) by light activation of a non-toxic photosensitizer. The advantage of the method is its selectivity for localized malignancy treatment. Quantum dots can be the photosensitizers or they can activate another photosensitizer by serving as energy donors (Bakalova et al., 2004; Samia et al., 2006; Gao et al., 2005).

Toxicity concerns

Although they show great potential for in vitro applications, a prime obstacle to the use of quantum dots for in vivo imaging is the concern over their semiconductor components, which are highly toxic. The main worry is the robustness of the surface coating. In addition, their clearance mechanisms from the body are unknown. Several studies, however, have reported using quantum dots in vivo with no detectable adverse effect to the model organism (Azzazzy et al., 2007).

Gold nanoparticles

Gold nanoparticles generally refer to both gold nanoshells, which consist of a thin gold shell surrounding a dielectric core composed of an insulating material such as silica, or simple spherical gold nanoparticles. They range in size from 0.8 to 250 nm and are characterized by high absorption coefficients (Liu 2006). They exhibit a unique phenomenon known as surface plasmon resonance, which increases their optical absorption and scattering by four to five orders of magnitude (Jain et al., 2007). When a gold nanoparticle is exposed to light, the oscillating electric field component of light interacts with the free conduction-band electrons at the surface of the gold nanoparticle, causing their collective oscillation, which is referred to as a surface plasmon. When the surface plasmons have a frequency similar to that of the excitation light, surface plasmon resonance occurs. This phenomenon is also responsible for the intense red colour of colloidal gold nanoparticles (Jain et al., 2007). Plasmon–plasmon resonance, resulting from the interaction of locally adjacent gold nanoparticle labels that have bound to a target, changes the red colour of colloidal gold to a bluish-purple colour upon colloid aggregation (West and Halas, 2003; Green et al., 2000). Varying the size, shape and composition of gold nanoparticles alters their optical properties. For example, changing the ratio between the thickness of the gold nanoshell and that of the inner core allows variation of the optical resonance of gold, shifting it as far as the mid-infrared region (West and Halas, 2003; Baptista et al., 2008).

Applications

The simplicity of synthesizing gold nanoparticles and their ability to functionalize their surfaces with different molecules, such as peptides, proteins and oligonucleotides, mean that gold nanoparticles are ideally suited to a range of biological applications. Their enormous visible-light extinction behaviour (Xie 2004) allows them to be tracked inside living cells using white-light illumination. The optical properties of gold nanoparticles, such as the surface plasmon resonance absorption band, are influenced by the particle size, shape, medium dielectric constant and temperature (Daniel and Astruc, 2004), giving gold nanoparticles the advantages of multi-colour tracking and assays using one light source.

Diagnostic applications

Lin et al. (2005) used gold nanoparticles to develop a microchannel immunoassay that detects antigens from the bacteria *Escherichia coli* and *Helicobacter pylori* antigens with a detection limit of 10 ng. The nanoparticles were conjugated to secondary antibodies specific to the biotinylated primary antibodies against the pathogens. Although the assay's sensitivity is comparable to that of dot-blot enzyme-linked immunosorbent assay (ELISA) and conventional dot-blot, the microchannel system is highly amenable to miniaturization. Hirsch et al. (2003) developed an immunoassay capable of detecting tiny quantities of various analytes including rabbit IgG in different media within 10–30 minutes, demonstrating the possibility of using the gold nanoparticles for whole-blood analysis.

Gold nanoparticles are also key components of the bio-bar-code assay (BCA), which has been proposed as a future alternative to the polymerase chain reaction (PCR) (Azzazzy et al., 2006), with zeptomolar (10–21 M) sensitivity for DNA detection. It has also been used for protein detection with attomolar (10–18 M) sensitivity. The BCA involves the isolation of target antigens by means of a sandwich process involving gold nanoparticles and magnetic microparticles that are both functionalized with antibodies specific to the target antigen. In addition, the gold nanoparticles are functionalized with barcode DNA. The great sensitivity of the BCA results from the effective sequestration of antigen and the amplification process that occurs as a result of the large number of barcode DNA strands released for each antigen-binding event (Azzazzy et al., 2006; Batista et al., 2008).

Therapeutic applications

Photothermal therapy is one of the most promising applications for gold nanoparticles. It could provide effective localized tumour destruction by conjugating the nanoparticles to tumour-specific moieties, to direct them to the tumour site. When short laser pulses are directed at the gold nanoparticles they release heat energy and destroy the tumour cells, which are more thermo-sensitive than normal cells (Huang et al., 2007).

Superparamagnetic nanoparticles

Superparamagnetic nanoparticles are made of magnetic materials such as iron, nickel, cobalt or alloys of magnetic metals. They exhibit superparamagnetism, that is, heat can change the direction of magnetization of the nanoparticles (Liu 2006; Neuberger 2005). They can be made biocompatible by coating them with a material such as silica or polyethylene glycol. For interaction with biomolecules, their surface can be modified by attaching ligands such as antibodies, proteins or oligonucleotides (Bryant et al., 2007).

Applications

Ibraimi et al. (2006) developed a rapid whole-blood magnetic permeability immunoassay for the detection of C-reactive protein (CRP). The assay used monoclonal anti-CRP antibodies conjugated to dextran-coated iron oxide nanoparticles as superparamagnetic labels and polyclonal anti-CRP antibodies conjugated to silica microparticles (to enhance the sedimentation of the complex). The increase in magnetic permeability of the sediment resulting from the presence of superparamagnetic nanoparticles is measured using an inductance-based transducer. The assay has a reported detection limit of 3 mg per liter and a total imprecision of 10.5%.

Superparamagnetic nanoparticles can be used as contrast agents in MRI and have much greater magnetic susceptibility than conventional MRI contrast agents, such as gadolinium. Ultra-small, superparamagnetic iron oxide particles used as contrast agents not only have greater magnetic susceptibility but also have more widespread tissue distribution because of their size, aiding their uptake in various tissues. Embedding iron oxide nanoparticles within polymeric matrices, such as dextran, starch, siloxane and polyethylene glycol, helps to stabilize them. MRI of the liver, spleen and gastrointestinal tract is an established clinical application of commercialized superparamagnetic iron oxide nanoparticles (Sonvico et al., 2005). Smith et al. (2007) demonstrated the utility of superparamagnetic iron oxide nanoparticles in the MRI evaluation of cardiovascular lesions and the simultaneous provision of morphological and biochemical data about them. In addition, Artemov et al. (2003) used streptavidin-conjugated superparamagnetic nanoparticles for magnetic resonance

molecular imaging of Her-2/Neu receptors expressed by breast-cancer cells. The receptors were tagged with biotinylated monoclonal antibodies, allowing the streptavidin-conjugated nanoparticles to bind to them. The contrast level of the magnetic resonance image was proportional to the level of expression of Her-2/Neu receptors. Moreover, superparamagnetic nanoparticles are useful for tracking cells and for calcium sensing (Jain 2007).

Conclusions

Several nanoparticle-based products are available commercially, mostly for in vitro diagnostics and imaging (Wagner et al., 2006). Nanoparticles can offer the medical field faster and more sensitive diagnostic assays, and more effective, controllable and directed therapies, as well as cost-effectiveness. PCR could soon lose its lead position as the gold standard for DNA detection to BCA, which pledges greater sensitivity. Gold nanoparticles can also open up a new arena in cancer therapy as photothermal therapy matures. On the other hand, quantum dots could help in photodynamic therapy. There are already in vitro diagnostic products in the market, based on gold and magnetic nanoparticles. Despite the fact that regulatory, safety and intellectual property issues are still unresolved, and the technologies themselves still need further optimization, nanoparticles are set to transform the field of medicine.

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26

Health Benefits from Artificial Membranes

Gilbert M. Rios

According to the World Health Organization (WHO's Constitution), health is a global and positive concept: 'A resource for everyday life, not the objective of living' (WHO 'Ottawa Charter for Health Promotion'-1986). Health care is the prevention, treatment and management of illness, as well as the preservation of well being, through a lot of services. In order to guarantee health care at reduced social costs, our modern societies use more and more sciences and technologies, not only with medicine and pharmacy, but also for water and effluent treatment, higher food quality, improved energy use …

Today the fast development and the increasing role of artificial membranes and related technologies strongly participate to these objectives, with a lot of applications as diverse as time-realized delivery of drugs, hormones and other medicinal substances through patches, tablets or capsules, artificial organs and tissue engineering, separation and reaction for pharmaceutical production, production of potable water, cold pasteurization of liquid…In a lot of countries at the forefront of science and technological development (USA, China, Japan…), this has led in recognizing artificial membranes as dominant technologies for our future.

You said 'artificial membranes'?

Life is based on biological membranes which basically are thin layers separating two media. Their function is to protect one medium from the other, while allowing selective exchanges between them. All the cells are surrounded by membranes; our skin is also a fantastic high-tech membrane…

Artificial membranes are simplistic industrially manufactured copies of these biological models. With them the exchanges are regulated by the external forces—as an example, a transmembrane pressure as for reverse osmosis (RO) or an electrical potential for electrodialysis (ED)—, the properties of the fluids—which ordinarily circulate in a tangential way as regards the wall to limit fouling and to increase the whole process/system efficiency—and the characteristics of the thin film material—which may be polymeric, inorganic or hybrid, dense or porous, neutral or electrically charged…—. The main performance criteria are the flux (which represents the quantity of fluid crossing the layer) and the selectivity (associated to the balance between the retained and non-retained species).

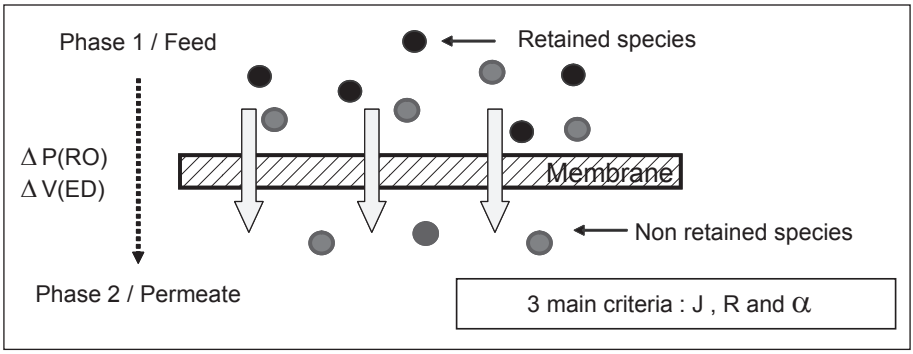

Figure 1 Basic principles of membrane separations

With cell membranes as an ultimate model, these breakthrough biomimetic approaches offer a privileged direction to reach sustainable development with improved citizen health and well-being. With the development of nanotechnology, new materials with nanoscale controlled properties have emerged, which seem promising to a really bright future.

In what follows, a few examples are presented, more specifically focused in the fields of:

- Medicine: artificial organs and medical devices
- Pharmaceutical industries: bio-separations
- Water production: sustainable and safe processes

Different points of view and approaches are privileged for the next paragraphs with successive entries via material, process and application aspects.

Mixed-Matrix Membranes (MMMs) as new promising materials

The mixed-matrix membranes are merely hybrid membranes consisting of nanoparticles imbedded into a polymeric matrix as represented on the following schema. The presence of nanoparticles allows getting much higher

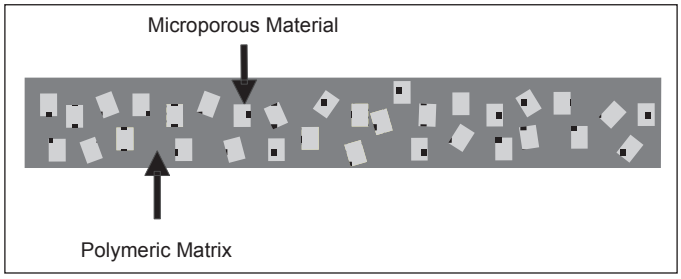

Figure 2 Schema of a mixed-matrix material

selectivity without compromising the flux. Different concepts are under investigation, which involve zeolites, carbon molecular sieves, other porous particles…or non-porous fillers. The selectivity is linked to the polymer free volume, the particle size and surface, the presence of covalent bonding…

MMMs fibers with small affinity particles entrapped, and easy accessibility for target molecules, have been recently proposed as a very extensive alternative to the most traditional route for harvesting proteins (precipitation + centrifugation, filtration and/or chromatography), particularly for the separation, recovery of recombinant proteins, antibodies (Twente University). Adsorption capacities and flow rates are much higher and better controlled

than in packed bed or expanded bed systems, leading to low consumption of energy, chemicals and water and to a friendly-environmental process.

Another example is provided by the new RO membrane presented by Eric Hoek from the University of California to reduce the cost of sea-water desalination and waste-water reclamation. It is a uniquely cross-linked matrix of polymers and nanoscale engineered particles, which creates molecular tunnels through which water flows much more easily than nearly all the contaminants. The highly porous nanoparticles are soaking up water like a sponge, while repelling dissolved salts and other impurities such as organics and bacteria. As a result, driven-pressure are lower than in conventional systems. The overall cost of desalination is considerably reduced by (25%), including energy demand and environmental issues. One must remember that water production and recycling is a key topic for California, the fifth largest economy in the world!

Nanofiltration (NF) a very quickly developing technology

NF is quite a new technology which allows the removal from a liquid of:

- Nanoscale uncharged molecules by size exclusion and/or from differences in diffusion rates
- Ions (mainly multivalent) by electric charge effects

Classical process characteristics are indicated in the following figure.

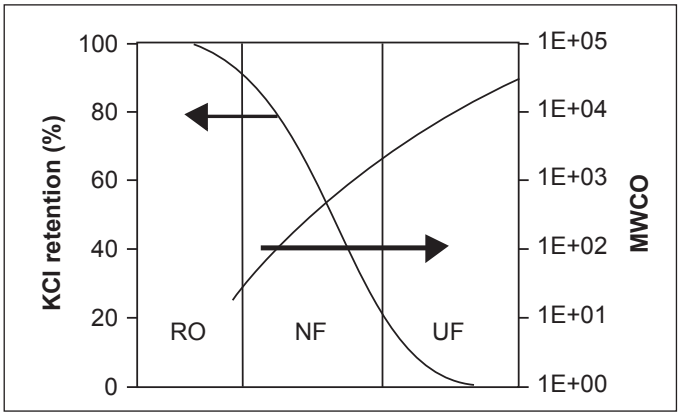

Figure 3 Typical retentions for KCl (salt) and organic species (MWCO) in Nanofiltration

For the last decade, one can mention among the main breakthroughs and more ambitious projects involving NF for improving drinking water quality:

- The reduction of hardness with softening processes; in that case NF was in competition with traditional ion-exchange systems or lime softening (regeneration, sludge and wastes…) and typical rejections of 70 to 90% were obtained
- The separation of natural organic material (NOM): today there are in the market various membranes with MWCO below 500 daltons, sufficiently low to remove the major part of humic and fulvic acids
- The high elimination of micro pollutants such as pesticides and organohalide compounds which have very negative effects on health (carcinogenic…); in that case, NF was in competition with activated carbon adsorption, a very expensive method (particularly in the presence of large fractions of NOM due to competition, regeneration…)

New very promising projects of technological developments are today focused on the abatement of fluoride ions to prevent fluorose disease, or the separation of arsenic, lead, aluminium and uranium. The maximum fluoride concentration in drinking water has been fixed by the World Health Organization at about 1.5-2.0 mg/l, while in some sub-Saharan Africa countries it may be higher than 20-25 mg/l. As (V) and As (III) are limited to 10 mg/l in France while in a lot of countries in the world concentrations higher than 50 mg/l may be found (not only in Bangladesh, India, China… but also in the USA). For such applications and large water production in rural countries, NF appeared to be more adapted than ion exchange, adsorption or biological treatment.

Other recent works are devoted to membrane bioreactor coupling with nanofiltration for an improved removal of toxicity in the hospital effluent. In hospital discharges, and more generally in water resources, there are numerous toxic pollutants (estrogenic hormones and other bio-products) which are responsible for cancers, allergies, fertility losses, thyroid diseases … Today there is no clear legislation anywhere in the world about this topic. By adjusting the contact time between the pollutant and the purifying biomass (MBR), it is possible to eliminate a large part of contaminants with strong biological/chemical resistance and/or low concentration; the addition of a further NF step to a MBR may eradicate the residual pollution.

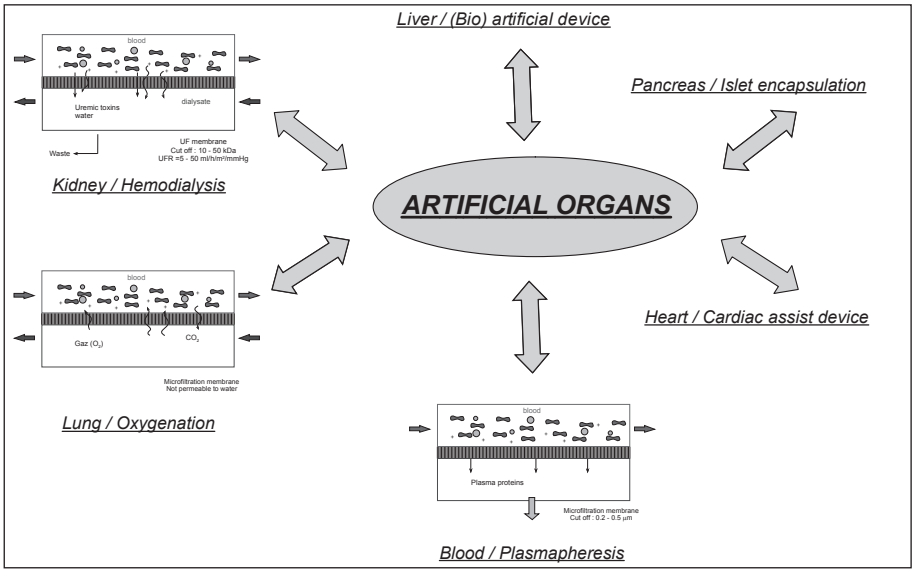

Figure 4 Schematic design of various artificial organs

A huge field of applications for membranes in medicine

The requirements for a «medical» membrane concern are as diverse criteria as mass transfer aspects -permeability, sieving properties, fouling potential-, biocompatibility -cell membrane interactions, protein adsorption and immune system- or sterility and single use. All this refers directly to structural and surface material properties, morphology, chemistry, thermodynamics or fluid dynamics.

With artificial organs, the membrane is used as a privileged tool to separate the medium to purify it from the extracting solution. For artificial kidney and hemodialysis, the main objective is to separate urimic toxins and water from blood with UF membranes as shown in the previous figure. Basic research in the field of dialysis started as soon as 1861; then renal replacement therapy and major concerns developed with 3 major steps:

- Sustaining life and making the treatment available for large groups of patients. Dialysers hand-made. Removal of low molecular weight uraemic toxins by diffusion only (1945-65)
- Increasing patient numbers. Availability and widespread application of industrially manufactured dialysiers. Compatibility and treatment tolerance

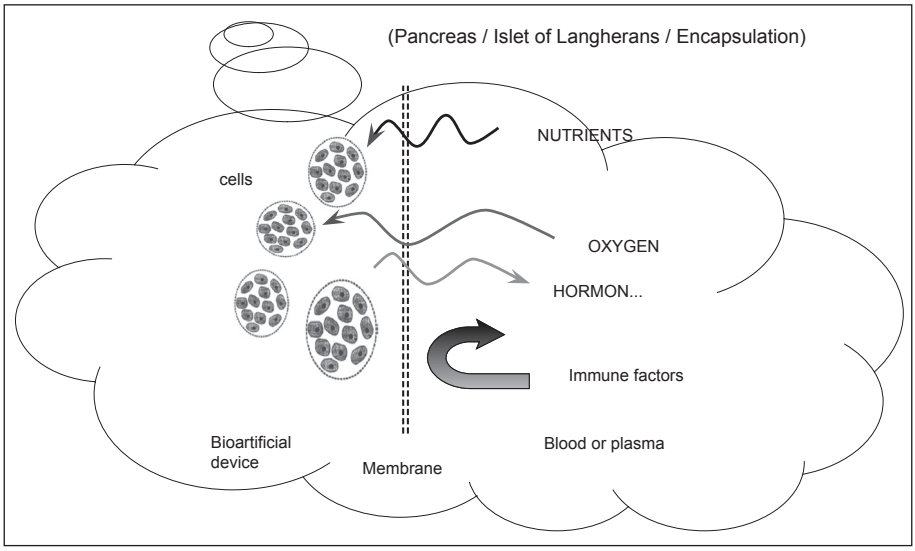

Figure 5 An example of bioartificial organ: the pancreas

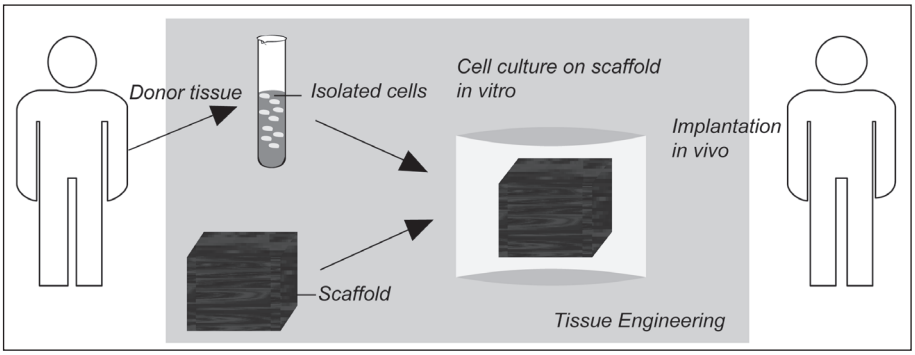

Figure 6 Cell culture and application

parameters. Removal of middle molecules and convection with more open membranes (1965-85)

- Quality considerations. Improving survival and quality of life for the patients. Ultimate aim: symptom-free treatment resulting in the long-term reduction of morbidity and mortality in chronic hemodialysis patients (1986-until now) … with a general trend to go towards more functionalized membranes

With bioartificial organs, the membrane aims to regulate the exchanges between encapsulated natural cells and the blood or plasma, allowing the transfer of nutrients, oxygen or hormones in the reverse side, while

preventing the crossing of immune factors. This is the case with the pancreas or liver.

At last, with tissue engineering a porous scaffold structure is required to guide the proliferation, growth and development of cell appropriately in three dimensions as shown in the following schema. Although scaffolds can be created using one of the many conventional techniques available, most suffer from a lack of mechanical strength and/or uniformity in pore distribution and sizes. Membrane materials have been successively used for this purpose.

Conclusions

Artificial membranes and related technologies represent definitely 'dominant technologies' for the future of all our societies, particularly for health in relation with environment and energy. They are fantastic tools for regenerative medicine, artificial organs, bio-separations and reactions in pharmaceutical industries, drinking water production… With cell membranes as an ultimate model, these breakthrough bio-mimetic approaches offer a privileged direction to improve citizen health and well-being. Today more than 300 million kms of hollow fibers are manufactured for hemodialysis every year; new plants installed in Israël, Saudi Arabia for desalination …have a total capacity of more than 200,000 m^3/day; the market is huge (a few tenth billions $ expected in 2010) and fast growing (8-12% a year)!

To be as efficient as possible, research and technological developments will ask for a strong and always renewed collaboration between the different actors: researchers, stake-holders, decision-makers… Holistic approaches based on strong integration of disciplines and expertise on a case-by-case basis will have to emerge and all kinds of synergies will be welcome. Among others and along with more classical bilateral actions, it seems that global instruments such as UNESCO through the actions of its chairs and centers, as well as the European Union through its various research and structuring programs, should play a main part in this whole process.

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Digital Molecular Medicine in Venezuela

Rafael Rangel-Aldao

The emerging field of systems biology is transforming molecular medicine and the entire health system to such an extent that it is making obsolete the old model of an isolated physician with a patient, replacing it with more effective global networks of collaboration. This new medicine can be viewed as a branch of information science that, combined with genomics and proteomics, is giving rise to personalized health care at the molecular level. It can predict and prevent the risk of major common diseases, and actively involves patients, or healthy individuals, in their own well-being (Hood, 2007). This is 'P4 medicine', so-called because it is predictive, preventative, personalized and participatory. It is essentially based on the social life of informational biological molecules that are arranged in complex networks following a power law by which a few nodes or hubs, made of either genes or the products of transcription and translation, dominate the entire network by their unequal distribution of links or edges (Barabasi & Albert, 1999).

Since 2007, a handful of publications of genome-wide association studies (GWAS) have shown how the genomic variations of some of these hubs can be applied to predicting the risk of multigenic and common diseases (Christensen & Murray, 2007). Moreover, combining GWAS with clinical and metabolic indices of risk, significantly improves the power of such techniques for predictive and personalized medicine (Kathiresan et al., 2008).

Here I will outline three hypotheses relating to this work:

- That biological information is essentially organized at the molecular level into small-world and scale-free complex networks where a few nodes (genes and proteins) become hubs that dominate the entire network
- That such knowledge, emerging from systems biology, can be translated into this new type of molecular medicine, which is predictive, preventative, personalized and participatory
- That this type of molecular medicine can be managed in a digital and scalable form to develop innovative health systems in developing countries, with significant economic and social payoffs

Organization of biological information

Systems biology has produced a new experimental approach to understanding how biological information flows and is regulated in living cells through complex networks (Kitano, 2002). Three features distinguish this new approach (Rangel-Aldao, 2007):

- The integration into one system, at the level of either cells or whole organisms, of more than 100 physiological processes occurring simultaneously (Westerhoff, 2005)
- A mathematical understanding of how the system works within complex networks encompassing a large number of molecular interactions that operate hierarchically or in parallel as highly integrated modules (Galperin, 2006) and are responsible for the adaptive states of the cell and organism (Kirchner, 2005)
- A fusion of biology with other branches of science, such as chemistry, physics, mathematics and engineering, including robotics and high-throughput technologies, to make it possible to understand and predict not only systemic properties but also their design (Bork, 2005); the subject matter of systems biology is therefore information (Hood, 2000)

There are two main types of network encompassing the flow of biological information: 'small-world' and 'scale-free'. These two complex networks are not mutually exclusive because some of the modular subsets or functional modules of large scale-free networks are actually small-world networks. Small-world networks are highly packed, exhibit lethality and centrality, and have short paths from the most distant to the central nodes (that is, from the periphery to those with more connections edges). In contrast, in scale-free networks, by virtue of the power-law distribution, as the network grows, the most connected nodes or hubs become richer in

connections or edges, and hubs tend to dominate the network. Scale-free networks also have a hierarchical architecture, are modular, have low error rates and exhibit vulnerability.

Although the evidence is still not entirely clear at either the cellular or the whole-organism level (Dupuy et al., 2006), a topology of scale-free networks is consistent with the observed networks of biological information in the genome (Luscombe et al., 2002), the proteome (Koonin et al., 2002), the metabolome (Jeong et al., 2000), and even the entire physiome (Buchman, 2000), which all seem to follow a power-law distribution where the richest node gets richer in edges or connections. Such structural arrangements imply that very few hubs made of genes or their encoded products would exert both centrality and modularity on the interconnected pathways of the cell's signal-transduction machinery, and as such they may be of considerable therapeutic value (Allarakhia and Wensley, 2007).

However, Khanin and Wit (2006) have disputed the power-law distribution of biological networks in their mathematical analysis of ten data sets of a range of biological interactions published in the literature. They found that they could not 'identify a single interaction network that has a nonzero probability of being drawn from the power-law distribution'. Their study nevertheless asserts that key features of biological networks, such as 'small world and lethality and centrality properties, still hold true independently of the precise mathematical form of the connectivity law and of their lack of scale-free behavior for all the datasets mentioned in this paper'. The knowledge to interfere or modify the biological information of a major hub may therefore be useful to obtain both diagnostic and therapeutic benefits from the functional modules of molecular interactions deep in the network (Hofmann et al., 2006).

From systems biology to P4 medicine

The existence of hubs comprising either genes or proteins that regulate entire networks or functional modules makes it possible to study a few targets at the molecular level as a way of following the flow of biological information that leads to disease in whole organisms, such as the human body. Such

hubs are known to be involved in a range of ailments, including the most prevalent diseases and those responsible for a large number of deaths and the global burden of disease (World Health Organization, 2008).

Four common diseases—cardiovascular disease, cancer, obesity and diabetes—account for 74% of the total cost of health care in the United States (Burrill, 2007) and 45% of global mortality (WHO, 2008). These figures are projected to increase by 2030, with cardiovascular disease and cancer being two of the top three global causes of illness, along with AIDS (Mathers & Loncar, 2006).

Cardiovascular disease, cancer, obesity and type 2 diabetes have a common path of biological information networks starting from endoplasmic reticulum stress and leading to a systemic immunological

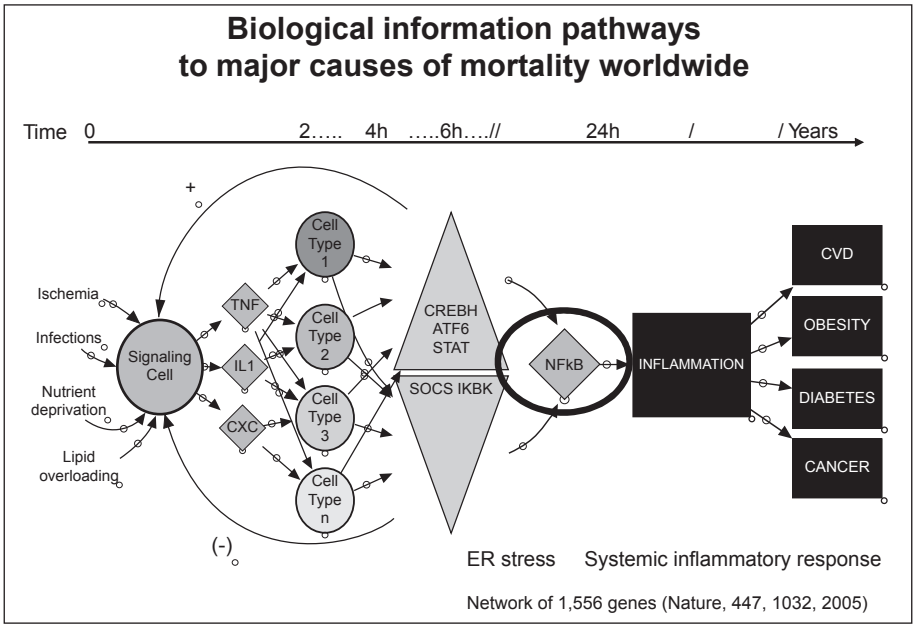

Figure 1 **Gene hubs dominate the flow of information of the systemic inflammatory response**. A host of inflammatory stimuli activate signalling cells to induce key genes such as those encoding TNF and IL1 and a family of cytokines (CXC) that upregulate key genes from the stimulatory (blue triangle) or the inhibitory (grey triangle) pathways of endoplasmic reticulum stress (ER stress). These genes induce or repress the gene hub NF-κB, a key regulator of the systemic inflammatory response involved in cardiovascular disease (CVD), obesity, type 2 diabetes, and cancer.

response and disease (Hansson, 2005; Coussens & Werb, 2002; Kaufman, 2002), as shown in Figure 1.

The implication of having common roots is that prevention could be exerted at an early stage, before inflammation, at the level of ER stress, and upstream of many information pathways leading to more serious and costly diseases.

Preventative medicine is coming about with the advent of economically feasible applications derived from GWAS. Such studies involve single nucleotide polymorphisms (SNPs) of both coding and non-coding DNA sequences, some of which correspond to gene hubs associated with cardiovascular disease and type 2 diabetes, such as Apolipoprotein E (ApoE) and PPAR-γ, (Wellcome Trust Case Control Consortium, 2007). In my own country, Venezuela, such techniques can be outsourced from private companies or universities in the developed world, or even from leading developing countries such as South Africa, India, China and Brazil, making it possible to predict a healthy individual's level of genomic risk to the four diseases listed above. Moreover, genomic information is currently available from GWAS about more than 100 loci associated with genomic variations involved in more than 40 diseases (Pearson and Manolio, 2008). However, such associations are in most cases far from deterministic and express probabilities of risk that can be altered by changes in lifestyle and environmental factors, or modified by more direct means, such as clinical intervention with therapeutics. As a result, predictive medicine can be honed with the aid of other predictive parameters, such as blood pressure, heartbeat data and body mass index, and other known metabolic factors, such as cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL) and triglycerides, as well as indicators of inflammation such as reactive C protein (RCP) (Kathiresan et al., 2008)).

These factors can be grouped into three vectors of risk. Clinical factors include family history and lifestyle habits, such as smoking, alcohol intake and level of activity, as well as direct measurements of blood pressure, body mass index, abdominal circumference and electrocardiogram results. Metabolic factors include clinical laboratory determinations of blood glucose (glycaemia), glycated haemoglobin (HbA1c), LDL:HDL ratio, C-reactive protein, homocysteine and blood chemistry. Genomic factors include the following SNPs that have been shown by GWAS to

have predictive value for cardiovascular disease, type 1 diabetes, type 2 diabetes, breast cancer, rheumatoid arthritis and prostate cancer: ApoE, ApoB, PPAR-γ, the transcription factor TCF7L2, the protein tyrosine phosphatase PTPN22, the breast-cancer genes *BRCA1* and *BRCA2*, the HLA class II histocompatibility antigen HLA-DRB1 and 8q24.

These factors can be visualized quantitatively by virtue of their convergence into one overall value for each of four different levels of risk, denoted by a colour code as shown in Figure 2.

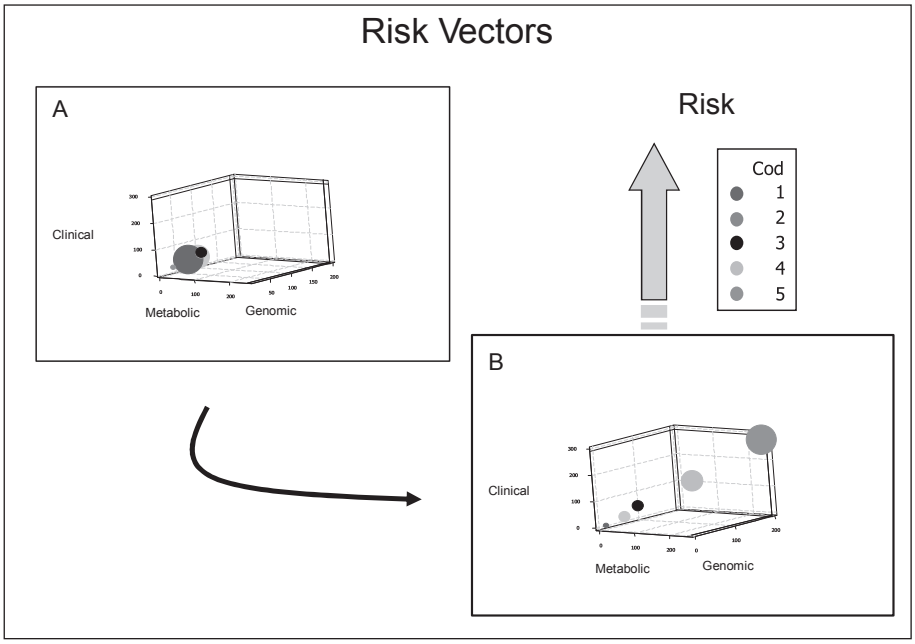

Figure 2 **Population analysis of the level of risk of cardiovascular disease,** cancer, obesity and type 2 diabetes. Colours represent levels of risk, from none (blue, level 5) to high (red, level 1). The volume of the spheres varies according to the frequency of individuals at each level of risk. (A) represents a population with a overall high risk, and (B) shows a population with a low risk.

Developing molecular medicine

The methodology outlined above makes it possible to assess and visualize the level of risk of entire populations by submitting volunteers to laboratory tests corresponding to both genomic and metabolic vectors, which must

be considered alongside their clinical results. If the results are in a digital format it is possible to generate databases that are amenable to statistical analyses and data mining. With these goals in mind, we have designed the Healthium Web, with a view to assessing the risk of major diseases in Venezuela. More importantly, it can be used to prevent or slow down the advent of disease through early intervention, both clinically and in terms of lifestyle, as depicted in Figure 3 below. The whole system is based on an Internet platform to establish direct links between the volunteers and doctors, scientists and lifestyle coaches.

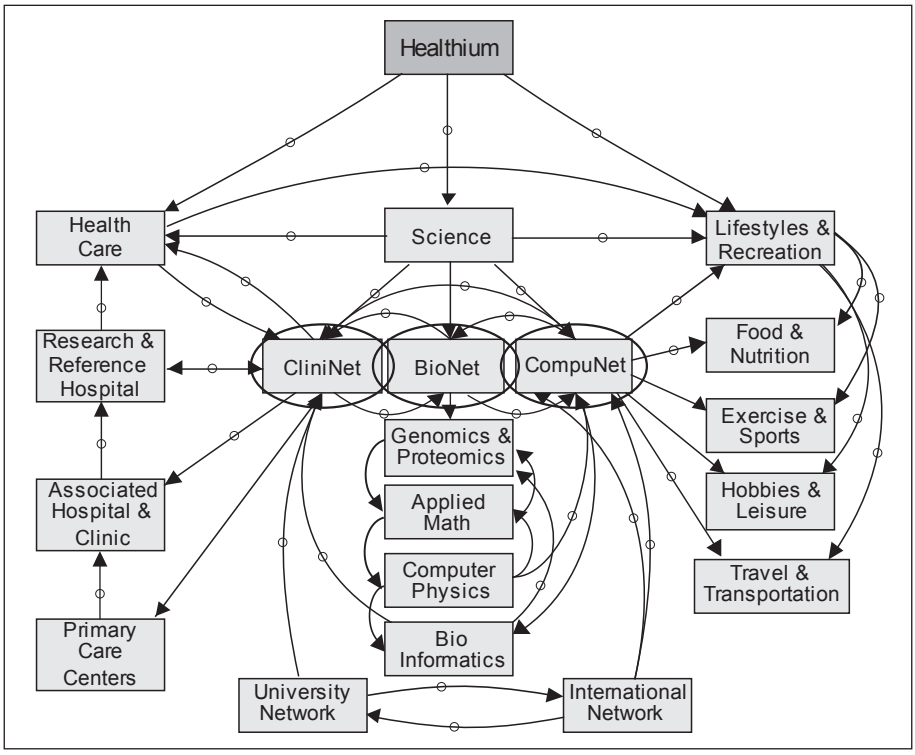

Figure 3 The Healthium Web Project to predict and prevent risk to major diseases. Science is linked to both health care and lifestyle by three connected networks of physicians (CliniNet), molecular biologists (BioNet), and computer scientists and mathematicians (CompuNet). The networks, linked to healthcare centers, recreation facilities, universities and centers of excellence, are responsible for submitting volunteers to testing that results in genomic, metabolic and clinical vectors of risk. Those at risk of disease can be treated or helped to make changes to their lifestyle.

The system is run by a start-up company called Genotron, which serves as a hub to link the scientific and healthcare networks with participating companies, as shown in Figure 4. Increasing the health of a company's employees in this way leads to a reduction of absenteeism and an increase in work productivity (Mills et al., 2007). Indeed, one third of the employees of most large US companies suffer from high blood pressure, high cholesterol, stress, being overweight, and have a poor diet and little physical activity (Kashima, 2006), all of which are risk factors for cardiovascular disease and type 2 diabetes (Wilson et al, 1998). Mills et al. (2007) calculated the financial impact of a health-promotion program on the employees of Unilever in Britain, and found that it yielded a return in a year of more than six times the amount invested in the health-promotion project.

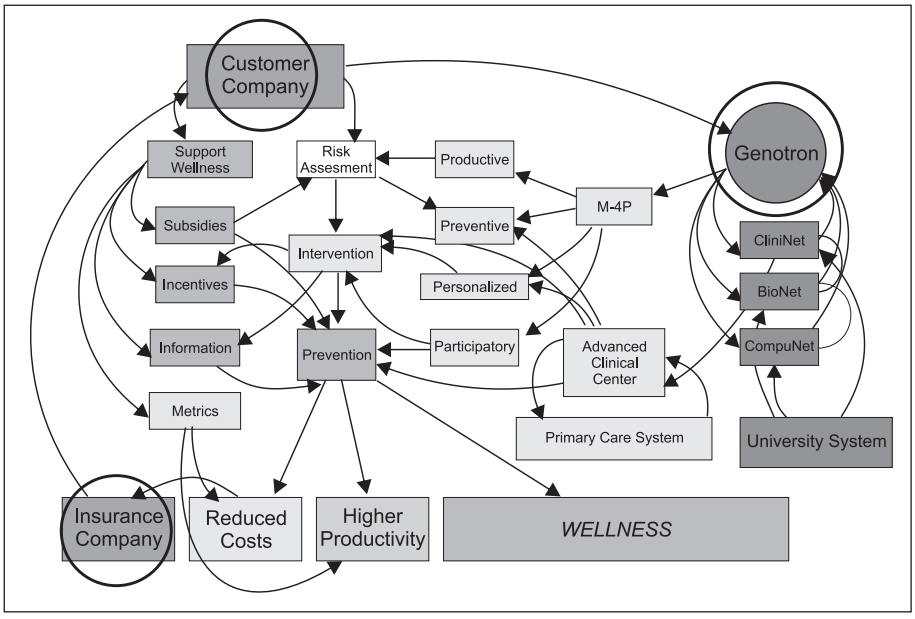

Figure 4 **Workflow diagram of the digital molecular medicine services provided by Genotron**. Genotron bundles the three networks, CliniNet, BioNet and CompuNet (Rangel-Aldao, 2005), connected to the university system of Venezuela and abroad, to provide predictive, preventive, personalized and participatory health care to the customer company. The service includes risk assessment and clinical intervention from a clinical center. The customer company helps the volunteers change their lifestyles to reduce their health risk.

Digital molecular medicine programs, such as the Healthium Web, allow the early assessment of the risk of major diseases in healthy individuals by combining the predictive value of genomic, clinical and metabolic vectors. To preserve the privacy of individuals, all subjects participate in the Healthium Web on a voluntary basis with informed consent and sign a contract that forbids the clinical network (CliniNet) from releasing individual information to employers. The employers will only have access to statistics regarding the overall extent to which their employees are at risk of major diseases, so they can put in place a program of incentives to increase the health of their employees.

After risk has been assessed for all volunteers, a program to support wellness is put in place through subsidies of primary health care and clinical intervention to treat, for instance, subjects with hypertension, lipid and sugar disorders, and obesity. In addition, a package to stimulate lifestyle changes rewards in the form of days off, travel expenses and access to leisure and sports. Such a program is currently underway with about 100 volunteers, and the results will be reported next year.

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5

SUSTAINABLE ENERGY AND A GREENER ENVIRONMENT

28

Bioenergy can Light up the World

João de S. B. Paes de Carvalho

About 2 billion people do not have access to energy in the form of mains electricity or gas. This stifles employment, productivity and industry, limits the value of production and results in deforestation, poor sanitation, illness, poverty, hunger and ignorance. The Worldwatch Institute (2005) declared the interplay of poverty, infectious disease and environmental degradation an 'axis of evil'.

The World Energy Council's Millennium Statement established three sustainability objectives, dubbed the three A's:

- Accessibility to modern, affordable energy for all
- Availability in terms of continuity of supply and quality and reliability of service
- Acceptability in terms of social and environmental goals

It also listed the requirements:

- Sustainability in terms of the environment and return of investment
- Prices that are affordable by the poorer classes
- Diversification of energy sources
- Fragmented production and distribution

But how can we achieve this? How can we go from promises to practice in bioenergy? Can biotechnology help, and if so, how?

We have developed a business-oriented, closed-loop concept for the efficient biomass-based production of energy (biofuels, biogas and electricity) and proteins that address the quest for environmentally friendlier energy, cleaner effluents and low-cost food. Biotechnology has

an important role to play. This concept is just one possible solution to the lack of energy in developing regions. Here I will outline the problem and show how it can be overcome.

The problem

In addition to the 2 billion people with no access to mains electricity, many more people have less than they need for modern agriculture and the production of goods, depriving them of a decent standard of living. When energy is scarce, production is extremely difficult, resulting in little employment, low productivity, little value to production and weak consumption markets. These areas also have environmental overexploitation, poor sanitation and health services, low standards of literacy and education, and suffer from hunger and poverty. The true 'axis of evil' really is 'the festering interplay among poverty, infectious diseases and environmental degradation' (Worldwatch Institute, 2005).

This is bad news for everyone, whether they inhabit these countries or live in more developed regions. The ripple effect of those poor conditions drains efforts to develop poor countries, depriving everyone of opportunities. It also results in hoards of immigrants at the borders of the developed countries, creating problems as their social systems overflow.

The Millennium Statement of the World Energy Council established three goals, called the 3 A's:

> '*Accessibility* means that a minimum level of commercial energy services (in the form of electricity, stationary uses, and transport) is available at prices that are both affordable (low enough to meet the needs of the poor) and sustainable (prices reflecting the full marginal costs of energy production, transmission, and distribution to support the financial ability of suppliers to maintain and develop these energy services). Getting access to the two billion people in the world without reliable commercial energy of any kind is the key.
>
> *Availability* relates to the long-term continuity of supply as well as to the short-term quality of service. Energy shortages can disrupt economic development, so a well-diversified portfolio of domestic or imported (or regionally) traded fuels and energy services is required. Keeping all energy options open is the key.

> *Acceptability* addresses public attitudes and the environment, covering many issues: deforestation, land degradation or soil acidification at the regional level; indoor or local pollution such as that from the burning of traditional biomass fuels, or because of poor quality coal briquettes or charcoal production; greenhouse gas emissions and climate change on a global scale; nuclear security, safety, waste management, and proliferation; and the possible negative impact of the large dams or large-scale modern biomass developments. Clean technologies and their transfer to developing countries is the key.'

The opportunity

With this in mind, my colleagues and I have developed a project called 'Bioenergy Integrated Projects', which I will outline here.

Brazil has considerable experience in the production of sugarcane-derived ethanol, which led to the Proalcool program in the 1970s that was based on replacing petrol in cars with ethanol. The program worked well, with about 98% of all new cars using ethanol. But as the price of ethanol from sugar rose relative to the oil price, the program lost some of its lustre and the trend was reversed.

The industrial base for ethanol manufacture from sugarcane was in place, however. When the price of crude oil roses again, the production of ethanol and cars with hybrid engines has increased, not with official government support but as a natural alternative to the cost of oil.

Today, Brazil is the most efficient producer of ethanol in the world, with an output of about 15 million cubic metres supplied by more than 300 mills. Brazil would be the world's largest ethanol producer if it were not for US subsidies to corn ethanol producers and US and European trade barriers.

There are several opportunities to improve production in an ethanol mill, and these are the focus of this project.

Traditional ethanol mills manufacture sugar and ethanol, and produce electricity in co-generation plants. The alcoholic fermentation produces about 715 kg carbon dioxide and 12–15 cubic metres of vinasse per cubic metre of ethanol. The co-generation plant also generates carbon dioxide, which is released to the atmosphere and is absorbed by the growing

sugarcane. The vinasse is spread as a fertilizer for the sugarcane, but its use is restricted by nutrient absorption rates in the soil and the cost for transportation between the mill and the field.

Traditionally, mills focus only on producing sugar, ethanol, yeast and electricity. The carbon dioxide and vinasse are merely by-products, and their potential is not explored. In the Bioenergy Integrated Project, we present ten opportunities for producing additional energy and food from a new-style ethanol mill, seven of which are new.

The project

One hectare of sugarcane produces about 7,000 litres of ethanol and enough bagasse (the fibrous residue remaining after the sugarcane is crushed to extract the juice) to generate 2.5 MW of electricity. The alcoholic fermentation process uses yeast, which ferments the sugar of the cane liquor to produce ethanol. After the fermentation, the yeast is used in an animal feed supplement.

The first new opportunity is the production of more energy by putting the vinasse through a biodigestion process and burning the resulting biogas, which is about 65% methane, in engines or turbines. Efficient biodigestion equipment has already been developed and its operation is dependent on the vinasse's chemical demand of oxygen.

The next opportunity is the production of improved fertilizer. The effluent of the biodigester is a better fertilizer than raw vinasse. The liquid effluent can be filtered to retain the solids, which can be spread on the fields.

The remaining liquid effluent can be taken to photo-bioreactors where algae will grow, fed by additional nutrients, carbon dioxide from the alcoholic fermentation and sunlight. The next opportunity involves harvesting the algae and processing them into an algae cake and oil. The liquid effluent will be used in the 'ferti-irrigation' of the sugarcane. The algae cake constitutes a protein-rich feed for animals and fish. It can be used directly or mixed into other feed as a supplement. It could eventually be transformed into a food supplement for people.

The oil can be transformed into biodiesel by the traditional process of transesterification. The next opportunity is a new biotechnological process

to produce better quality biodiesel more cheaply. The biodiesel produced will not contain traces of the chemicals used in the transesterification, and the glycerin by-product will be much purer.

The next opportunity is the production of glycerin, which can be sold as it comes out of the process or purified. Glycerin, in the absence of a commercial destination, can be directed to the biodigester, where it will improve the output of methane, increasing the amount of energy produced.

The next opportunity is the transformation of glycerin into animal feed by a fermentation process that is currently being developed. In our experiments, it has yielded one kg of feed per kg of glycerin used.

The final opportunity relates to the carbon credits obtained under the Clean Development Mechanism of the Kyoto Protocol. The carbon credits can be obtained in two processes: the electricity generated by the burning of biogas, instead of fossil fuel, and in the biodiesel that will be used instead of diesel oil.

To summarize our Bioenergy Integrated Project: The vinasse of the alcoholic fermentation is biodigested producing electrical power and fertilizer; the liquid effluent, carbon dioxide and nutrients produce algae in photo-bioreactors; the algae are processed into feed and oil to become biodiesel; the glycerin by-product is processed into animal feed; and, finally, carbon credits are obtained for the power and biodiesel produced. As you can see, it is a closed-loop process, where the effluent and the by-product of the previous process feeds the next stage of production—there is little waste.

Results

The most important results of the project are the creation of jobs, electrical power to supply the surrounding communities, and the economic development of the areas where the integrated mills will be installed.

In our stimulation of an agro-industrial complex comprising a plantation of sugarcane and an ethanol mill to handle 1,500,000 tons of cane, the Bioenergy Integrated Project will create about 1,500 direct jobs and supply electricity to up to 100,000 people. The estimated total investment

required to build a plant, excluding land costs, is about US$250 million. Such a plant would be expected to produce 127,000 m^3 of ethanol, 17,000 m^3 of biodiesel, 300,000 MW of electricity, 80,000 tonnes of fertilizer and 45,000 tonnes of animal feed.

Another advantage of the Bioenergy Integrated Project is that all the processes used are environmentally friendly and sustainable. It reduces the emission of greenhouse gases, and the liquid effluent from the cultivation of algae needs almost no treatment to be used as a fertilizer or discarded in nature. The algae produced are fully used as feed or in the production of oil for biodiesel. The biodiesel production process will be free of chemicals and the glycerin by-product, which is currently difficult to dispose of, can be used as animal feed.

Requirements

What conditions are required for the Bioenergy Integrated Project to be established?

First, we need scientific improvements, as many of the processes used require further development. We already have the necessary technology for the sugarcane plantation, the mill and the biodigestion process, so the project can be partly built today while the new opportunities are fully developed.

Second, the sugarcane and microalgae require certain environmental conditions if they are to grow efficiently.

Third, we need political will, as the basic regulations and legislation, covering environmental and commercial aspects and taxes, and the basic infrastructure, such as roads, electrical distribution network and trained labour, all need to be in place to make investment feasible.

Fourth, we need investors, as the project requires a substantial amount of funding and, as with any agro-business, there is a certain amount of risk.

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The Potential of Biofuels for Egypt

Salah E. Hassouna

The term 'biofuels' has emerged in recent years to refer to sources of energy derived from biomass — even though our traditional sources of energy also use biomass. In recent times, petroleum oil has been the world's major source of energy, but it is not renewable and our resources will one day be depleted. Soon after oil was discovered, its cost was very modest; however, the oil embargo in 1973 caused oil prices to increase, and there have been further price rises recently. From 1978 to 2001, the price of crude oil rose by 69% to US$22 per barrel. From 2001 to 2006, it rose by 150% to US$55 per barrel, a much greater rate of increase. By April 2008, the price was US$145 per barrel. It is easy to see why many countries are looking for alternatives. Of course, wood and coal are still available, but they lack the convenience and flexibility of oil. Other sources of energy, such as hydropower, wind power, nuclear, geothermal and solar energy, are either more expensive or need technologies that are not widely available. So attention is turning to biofuels.

Biofuels are produced by the conversion of biomass to other chemicals that store energy, such as biogas, or by using sugar crops as a basis for fuel, such as bioethanol. The aim is to get a product that is both efficient at using the energy content of the biomass and convenient to use. Various liquids and gases lend themselves to different applications.

Here I will discuss the current position of bioethanol, biogas, biodiesel and biohydrogen. I will then consider the energy situation regarding my own country, Egypt.

Bioethanol

Bioethanol is produced when certain microorganisms ferment sugars; the ones that are widely used are the yeast *Saccharomyces cerevisiae* and the bacteria *Zymomonas mobilis*. Traditionally, this process uses only hexose sugars, although hemicellulose, which is mainly composed of pentose sugars, can now also be used in bioethanol production. The raw materials differ in their cellulose and hemicellulose content, as Table 1 shows.

Table 1 The chemical content of sources of bioethanol.

Material	% Cellulose	% Hemicellulose	% Lignin
Hardwoods	40–55	24–40	18–25
Softwoods	45–50	25–35	25–35
Leaves	15–20	80–85	0
Cotton	80–95	5–20	0
Newspaper	40–55	25–40a	18–30

In order to render these raw materials amenable to ethanol production, a hydrolysis step is needed before fermentation can occur. Enzymatic and acid hydrolysis are both widely used across the world. The enzymatic hydrolysis of cellulose requires enzymes known as cellulases, which are naturally produced by numerous organisms. The most important enzymes commercially are endoglucanase and cellobiohydrolase. Acid hydrolysis usually uses sulphuric acid, as it economical to use and the remaining acid can be neutralized with gypsum salt. The starch can be hydrolysed enzymatically by amylases after being pretreated with by heat. Some amylases can withstand high temperatures, reducing the need for cooling.

Fermentation yields a broth containing just 5–20% ethanol, which undergoes fractional or azeotropic distillation to obtain fuel-grade product.

Bioethanol has been produced from sugar crops for some time. Brazil was one of the pioneers of bioethanol production, as an abundance of agricultural land and water (rainfall can exceed 2,000 mm per year) made it economically attractive. The sugarcane roots remain in the ground and the leaves are separated and burned, with the ashes left in the field as fertilizer.

One hectare of sugarcane yields up to 7,000 liters of ethanol per year, which compares favourably with other crops, such as sugarbeet (5,000 liters per hectare), corn (3,500 liters) and wheat (2,000 liters).

Biotechnology has helped to boost bioethanol production tremendously. For example, hydrolysis enzymes in the yeast allow them to use the raw materials directly. The genes that encode the enzymes endoglucanase and cellobiohydrolase were cloned in a stain of the fungus *Trichoderma* by protoplast fusion to improve their performance. Another improvement is the incorporation of osmotolerance genes in yeast, which allows higher sugar concentrations to be used at the start and a higher ethanol yield. Another breakthrough has been the development of *Escherichia coli* bacteria that can produce ethanol. Likewise, the regulation of the phosphotransferase system has increased the efficiency of the transport and utilization.

Biogas

Biogas is the product of anaerobic fermentation, or 'aerobic digestion', of waste matter such as sewage, garbage or manure by a variety of different bacteria. It is a mixture of methane and carbon dioxide, and can either be used in this form or purified to remove the carbon dioxide. The biogas yield varies in quantity and quality according to the raw material used as shown in Table 2.

Table 2 The quality and quantity of biogas depend on the raw materials.

Material	Digestion time (days)	Methane (m3 per kg)	% Methane
Sewage sludge	8	0.34	78
Garbage	6	0.38	62
Abattoir waste	13	0.35	74
Processed food waste	2	0.42	85
Animal manure	12	0.21	80
Plant residues	4	0.40	85
Reeds	18	0.25	77

The gas produced is used in several countries for the production of electricity or in a combined heat and power system, such as the Mogden sewage treatment works in west London. Many cities get some of their electricity from the anaerobic digestion of household solid waste. Biogas can also be produced from the degradation of organic waste in landfill sites. Even industrial wastewater can be a source of biogas production; a team from Alexandria University in Egypt showed that a system using whey as a raw material could save almost one-third of the energy used in the dairy industry.

Integrated systems that treat different waste products have been envisaged, and these have the benefit of algal growth, which thrive from heat from the power plant. An integrated system using garbage and wastewater for energy production along these lines has been suggested for the city of Port-Said in Egypt (Figure 1).

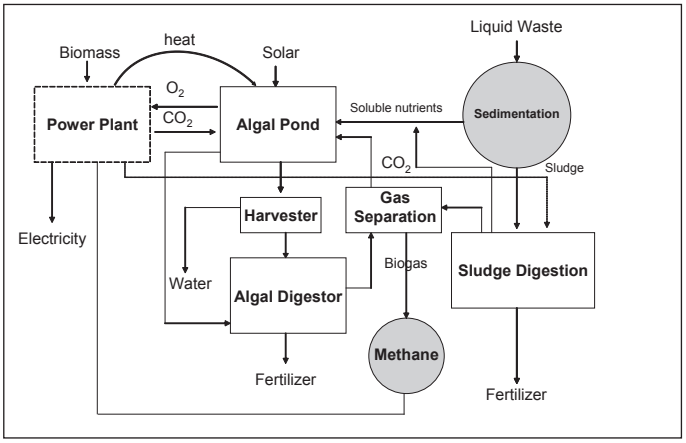

Figure 1 An integrated system for the production of biogas and electricity.

Biodiesel

Considerable research and investment have helped the spread of biodiesel, which is relatively easy to produce—some people even advocate making your own at home. The process can use oils and fats from various sources, including plant oils (such as *Rapeseed*, *Jatropha* and *Jojoba*), oil that has been

used for frying food, waste fats and oils from the food industry and oils extracted from algae. The oil undergoes esterification and transesterification to produce biodiesel and another valuable product, glycerol (Figure 2).

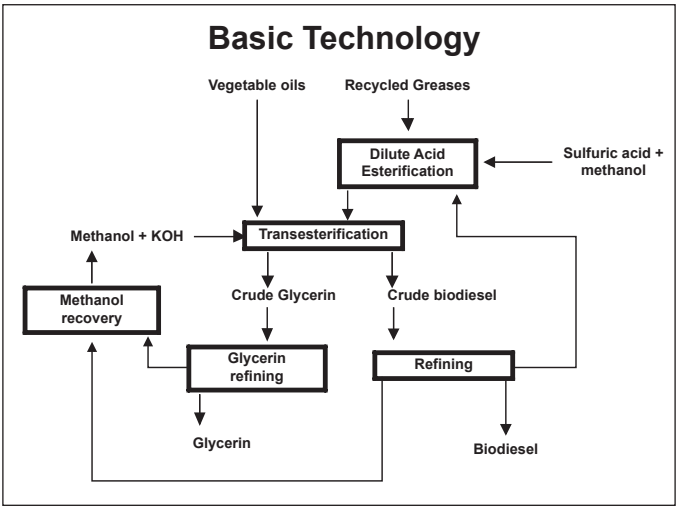

Figure 2 The production of biodiesel.

Biodiesel can be used alone or in blends. It is more environmentally friendly than petrol diesel as it produces less pollution in terms of carbon monoxide, hydrocarbons and particulates.

Biohydrogen

Several countries have strong research programs for the production of hydrogen by bacteria and algae from biological sources, or by using enzymes from nitrogen-fixing or anaerobic microorganisms. No commercial production of biohydrogen has started yet, but the emerging technologies appear promising.

Biofuels in Egypt

Egypt has limited land and water resources, so it is not feasible to grow crops such as sugarcane or cereals for the production of biofuels, but its vast coastline along the Red Sea and the Mediterranean could be used to site algal farms. The current plan is to use about 23 million tonnes of agricultural plant residues and 4.8 million tonnes of animal waste for the production of biofuels. Egypt also hopes to use treated or partly treated wastewater in for the planting of jatropha, for use in biodiesel production. The Egyptian PetroChemicals Holding Company has announced a plan for a production of 1 million tones of biodiesel by 2011.

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Environmental Safety of GM Crops

Eric Huttner

Our current standard of living depends on our ability to produce good-quality affordable food, feed and fibre, but we must also preserve the biosphere's capacity to do this for future generations. Crop improvement will play a major role in solving this challenge. The application of biology and biotechnology has been contributing to crop improvement for decades, through better breeding methods and more recently through the genetic modification of plants. But does the use of these biotechnological innovations in our agricultural production systems pose a specific hazard for the environment?

The perspective adopted here is that the ecosystem has to be managed in a sustainable manner; an environmental hazard is something that threatens this sustainability. An example of a serious threat to environmental sustainability is the recent increase of greenhouse gases in the atmosphere. This has mostly been caused by recent human population expansion and the large amount of energy used by a fraction of that global population.

Other perspectives could be adopted, such as requiring the complete preservation of the environment. From this viewpoint, any human impact would be considered undesirable. However, that seems to be a step too far.

My approach to the environmental safety of agricultural biotechnological innovation is as an interested witness with some professional experience in the field, including some involvement with genetically modified plants. My main activity in the past seven years has been to assist plant breeding by using

molecular markers, which does not involve genetic modification, so my current perhaps leaves me on the fringes of agricultural biotechnology.

I will present my views on how these questions and issues should be addressed, rather than try to provide definitive answers. It is my aim to promote thinking and discussion on this important topic, based on facts and realities that can be studied and assessed scientifically. The only safety issue is will discuss is environmental safety, but the principles apply to other areas of safety assessment.

Making decisions about environmental safety

The impact of agriculture on the environment has been massive. Humans have regularly introduced innovations into agricultural systems, and they have all affected the environment to some degree. It is critical that any innovation we deploy improves sustainability, but making decisions in this area is fraught with difficulties.

Here I will distinguish between two areas in this field of environmental safety:

- Avoiding taking the wrong path (for example, by adopting unsustainable practices)
- Avoiding making a mistake (accidents)

Environmental damage through unsustainable practices

Deforestation is a good example of an unsustainable practice. Defining sustainability and identifying unsustainable practices is complex, context-dependent and related to political and socio-economic issues, rather than scientific and technical issues. There may be many reasons why societies choose to deforest. It may be the wrong path, but not for everyone, and maybe not immediately. Another example is the farming of shrimps in Southeast Asia in fields previously used to grow rice. Again this raises complex issues about who benefits from the innovation, and what are the short- and long-term costs and benefits of adopting the innovation.

It seems to me that avoiding taking the wrong path is essentially a social and political issue, not an innovation issue. Empowering people to have the broadest possible participation in decision-making is one component

of avoiding wrong paths. Another critical component is to include in the decision-making process due consideration of long-range and long-term effects.

In this context, I believe that biotechnological innovations in agriculture are not fundamentally different from other innovations, such as the adoption of new species or changes to the agricultural production system. Therefore, in the absence of specific reasons to treat them differently, the adoption or rejection of biotechnological innovations on the basis of their effects on sustainability should be managed in the same way as the adoption (or not) of other innovations.

Environmental damage through accidental mistakes

The introduction of the cane toad in Australia as an agent for the biological control of a pest of sugarcane is a good example of an innovation mistake: it did not work, and it caused environmental problems.

To avoid making mistakes, the environmental safety assessment of biotechnological innovation can be conducted on a practical basis, as the issues can be spelled out in a specific manner. Biotechnological innovations in agriculture are mostly improved crop varieties, whether obtained through biology-assisted plant breeding or through genetic modification. They will affect the environment through the production system they are deployed in. This is the context in which the environmental safety of biotechnological innovations should be carefully assessed and regulated.

The use of herbicide-tolerant canola in Australia provides an interesting example. Until 2008, all canola produced in Australia was not genetically modified. About 60% of the canola planted in 2006 was tolerant to Triazine herbicides and 10% was tolerant to Imidazolinone herbicides. Genetically modified varieties resistant to other herbicides became available in 2008. The assessment of their environmental safety should address their specificities, for example:

- The properties and environmental impact of the herbicides used with these genetically modified varieties
- The likelihood that these varieties will spread in the environment as weeds
- The likelihood that the resistance gene will transfer to wild species
- The environmental impact that this gene transfer would have (if it were to happen)
- The likelihood that weeds would become resistant to the herbicide used

These issues are not new: they have been addressed in the past for non-genetically modified herbicide-tolerant canola plants. But they must be addressed again to determine the environmental safety of the biotechnological innovation represented by the genetically modified canola. In the absence of identified specific risks, it does not seem necessary to apply to the genetically modified varieties a different set of environmental safety requirements than those applied to the existing plants.

Societal requirements may change with time, or new information become available. If specific reasons come to light why previously used innovations should no longer be used, on the basis of an unacceptable environmental impact, this would apply to all specific innovations, whether they are biotechnological or not.

What if we make mistakes?

Imperfect knowledge and an inability to fully predict the future means that there will always be residual risks of mistakes in adopting innovations, biotechnological or otherwise. Short of not innovating, which means adopting the status quo as the best possible situation, there is no alternative to the careful assessment of innovations. Therefore, like all other innovations, agricultural biotechnology has to be assessed for its environmental impact, and adopted or not based on that assessment. However, a narrow focus on biotechnology as a source of innovations that are intrinsically dangerous for the environment runs the risk of missing other, possibly more important, environmental risk factors of current or future innovations. It may also lead us to delay or forego many of the environmental benefits that biotechnology may offer to agriculture.

New molecular markers for more efficient plant breeding

Harnessing better and wider genetic diversity to improve crops will contribute to a more productive sustainable agriculture. My own company, Diversity Arrays Technology, has a high-throughput, high-resolution and low-cost genome-profiling method that can help plant breeders invent

the safe, improved varieties of tomorrow. It will also contribute to the identification and management of genetic diversity in cultivated and wild species. And it will provide an effective tool to monitor gene flows, an important area of environmental safety assessment.

Conclusions

The impact of humans, including our agricultural impact, on the environment is becoming a major issue, affecting the life of all humans on the planet, with wide-ranging effects. It raises doubts about the sustainability of some current agricultural practices. Changes to the lifestyle of people in developed countries are probably inevitable. Preserving a future world worth living in means improving the life of people in developing countries while increasing sustainability overall. Agricultural innovations have a role to play in addressing these challenges, and they should be evaluated both for their contribution to the improvement of people's lives and for their impact on overall sustainability.

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Biotechnology and the Environment in Japan

Kenji Kurata

The progress of biotechnology in recent years has been astounding. Consider how the speed of genome sequencing has accelerated since the Human Genome Project. There are suggestions that a human genome could be fully sequenced for as little as US$1,000 by the year 2020. Just think what might be possible if individuals could know their own genome sequence.

Or consider the success of induced Pluripotent Stem (iPS) cell generation, which was demonstrated by Shinya Yamanaka of Kyoto University, Japan. Human cells that have already differentiated, such as cutaneous cells, can turn into stem cells when particular genes are introduced into the cells. The newly created stem cells are said to be pluripotent because they have the ability to differentiate into various different kinds of cells, such as cartilage cells. These differentiated cells could be used in medicine, for example, to treat cartilage problems when fresh cartilage cells are required. The generation of iPS cells is expected to open the door to extremely advanced medical care, such as regenerative medicine.

But biotechnology is not limited to the world of genes, cells and medicine. It covers various fields with applications in food, agriculture, energy and the environment. In developing countries, biotechnology can help to deal with infectious diseases, water purification and the shortage of food. Moreover, biofertilizers, biofuels and the bioremediation of soil and lakes can also be used to benefit developing countries.

It is all very well having biotechnology, but the next challenge is to introduce it to society to improve people's welfare and quality of life.

Framework for using biotechnology in Japan

In the field of health care, biotechnology is embodied in pharmaceuticals and medicine before being provided to society. The process of manufacturing pharmaceuticals uses various technologies, such as recombinant DNA, cell fusion and tissue culture. The effects of recombinant DNA, for example, were largely unknown when it was first introduced, but it was accepted because it was strictly limited to closed systems, such as confined reactors, where the technology is securely contained.

However, once a technique enters the environment, this raises various questions. A typical application of biotechnology in the environment is the use of genetically modified (GM) plants in agriculture. In this case, there is controversy over two different viewpoints; one is based on human safety, and the other is an environmental point of view. With respect to human safety, Japan's regulatory authority is imposing a safety assessment of GM food based on the concept of 'substantial equivalence', as in other countries (Organisation for Economic Co-operation and Development, 1993). Regarding the environmental issue, Japan's 'Law Concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms' regulates the use of GM organisms in both closed and open systems. Its objective is conservation and the sustainable use of biological diversity. The law was introduced in connection with the ratification of the Cartagena Protocol on Biosafety to the Convention on Biological Diversity, so it is referred to as the Cartagena Law. Before the Cartagena Law was introduced in 2004, there was no legal framework concerning the use of GM organisms in Japan.

The Cartagena Law focuses only on the use of GM organisms. Anyone who intends to use GM organisms in Japan must first obtain permission from the government, whether it is a closed or an open system. In both cases, the minister in charge will carefully review the application with respect to the potential adverse effect on biological diversity. Open systems are more likely to cause adverse effects, so ministerial approval is less likely to be granted.

Obtaining permission for use in Japan

The numbers of confirmations are given by the Minister of Economy, Trade and Industry for the industrial use of GM organisms in closed systems. These confirmations generally relate to the manufacture of industrial enzymes, reagents and pre-pharmaceutical materials. Almost 700 confirmations have already been issued for industrial use, all of which are for using GM microorganisms. In addition to this confirmation scheme, there is the concept of Good Industrial Large Scale Practice (GILSP). Combinations of certain host–vector systems and inserted DNAs are shown on the GILSP list along with safety requirements for facilities in which the GM microorganisms are used. No ministerial confirmation is required as long as the use of GM microorganisms is conducted under the conditions shown on the GILSP list. Once a ministerial confirmation is given for a certain system, this system will be added to the GILSP list with the consent of the applicant.

As well as requiring confirmation from the Minister of Economy, Trade and Industry, the manufacture of pharmaceuticals requires separate confirmation from the Minister of Health, Labour and Welfare, and food manufacture requires confirmation from the Minister of Agriculture, Forestry and Fisheries. Based on these schemes, GM organisms are widely used in closed systems in Japan. So far, no major problems have occurred, and their use has not been controversial. The use of GM organisms in closed systems is therefore accepted in Japanese society under the regulatory framework presently imposed. Indeed, virtually the same framework has been in place since the mid-1980s, when it took the form of voluntary guidelines, becoming a mandatory regulatory framework in 2004.

Most of the approvals of GM crops in Japan relate to the use of GM plants for both R&D and commercial purposes. A few approvals relate to the use of viruses in clinical trials, where they are used to introduce certain genes to patients for their treatment. The patients usually stay in a hospital, and the hospital room is regarded as an open system. Neither animals nor other microorganisms have been used in open systems in Japan so far.

As far as GM plants are concerned, more than half of the approvals are related to grains, but some are related to flowers. This is because there is a private company in Japan that is trying to create blue carnations and roses

by using a recombinant DNA technique. It has succeeded in creating blue carnations, and these are now sold widely. Blue roses are in the final stage of commercialization.

The commercialization of crops

The Minister has already approved some GM crops for commercial use according to the Cartagena Law. However, no GM crops have yet been grown commercially on Japanese soil. Even national institutes face difficulties when they try to grow GM plants in the open air for R&D. Some people claim that planting GM crops in the open air has adverse effects on biological diversity and causes 'gene pollution'. Sometimes lobby groups try to influence policies by changing public opinion. They are particularly effective at influencing local governments, as was the case in Hokkaido, for example. Hokkaido is the northern part of Japan, and is famous for producing high-quality crops. The local government there opposed the planting of GM crops because it was afraid that consumers would have a negative image of the local produce if GM crops were grown there. The Hokkaido government therefore established a municipal by-law. It has not banned the growth of GM crops directly, but it has effectively prohibited their growth by imposing heavy burdens, such as requiring that any GM crops be kept a long distance from non-GM crops. These regulations also apply to the growth of GM crops for R&D. Several local governments are now introducing similar regulations.

The public accepts this position, but no serious discussion has been conducted on this topic among ordinary people in Japan, and most people have not given the matter much thought. The population does not suffer from a lack of food, and Japan can import plenty of non-GM food from all over the world. If Japan was to have difficulty finding enough non-GM crops, then the issue of whether to accept GM crops would have to be considered more seriously by the Japanese people.

Japan is one of the wealthiest countries in the world, so it can afford to pay a premium for non-GM food. Developing countries do not have this luxury. They must accept GM food to solve their food shortage, and even then many people face starvation.

The problem with risk assessments

There is one more important issue to be discussed: the use of microorganisms in open systems. As mentioned above, the use of GM plants and viruses in open systems has been approved in Japan, but other GM microorganisms have not been approved for use in open systems. That approval would be needed for applications such as the bioremediation of soil and lakes, water treatment, biofertilizers, compost, the prevention of algal blooms, and so on. These applications could potentially solve a range of problems faced by developing countries.

Unfortunately, no firm methodology for risk assessment has been established internationally, even though the Cartagena Protocol requires risk assessment to be carried out before the first release of GM organisms. Under the Cartagena Protocol, the objective of risk assessment is provided as follows: to identify and evaluate the potential adverse effects of living modified organisms on the conservation and sustainable use of biological diversity in the environment, taking into account risks to human health. Note that this is an objective, not a methodology. There is no mention in the Cartagena Protocol of a methodology to attain this objective.

This lack of a methodology even causes problems when using non-GM microorganisms in open systems. In Japan, the government has bioremediation guidelines to ensure a certain level of safety for the release of non-GM microorganisms in open systems. Ministerial confirmation will be issued if microorganisms will have no adverse effects on biological diversity. Under this scheme, only two confirmations have been given so far. Both cases related to the use of well-known microorganisms, so the safety evaluation was not difficult. However, for more complex cases, the safety evaluation is extremely difficult without a concrete methodology for the risk assessment. This is why only two confirmations have been given and the use of microorganisms in the open air has not progressed.

Conclusions

The environment is constantly changing through genetic exchange, population dynamics, climate, and so on, without intentional human

intervention. So how can the adverse effects of introduced GM organisms be evaluated against a changing environment? If this problem is not solved, a concrete methodology will not be established, and the environmental application of biotechnology will stumble.

One possible way of breaking this deadlock is to develop the idea of 'substantial equivalence', which provides a scientifically sound principle of safety assessment based on the idea that existing foods can serve as a basis for comparing the properties of GM foods with the appropriate counterpart. This concept has opened a pathway for the development and commercial use of GM crop plants. For the practical use of these technologies, we need to establish the basic concept of an environmental impact assessment. In this context, it is time to consider a principle that guides the assessment of non-targeted effects of the unconfined use of biotechnology. We can then explore the concept of substantial equivalence for the environmental application of biotechnology.

It is becoming increasingly clear that life on Earth is threatened by changes to the climate and the environment. The introduction of modern biotechnology into society can potentially solve many of the problems facing the world, but its potential has not been sufficiently explored, for the reasons mentioned above. We have to go forward with the consent of society, and establishing a concrete methodology for a risk assessment on GM microorganisms released in the environment is a first step to creating public acceptance of biotechnology.

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Ozone, Climate Change and Plant Growth

Samia A. Madkour

Ozone is a colourless gas that plays a central role in atmospheric chemistry: ozone levels affect the climate, and the climate in turn affects ozone levels. In upper region of the atmosphere, the stratosphere, ozone shields the planet from harmful ultraviolet radiation. In the lower part of the atmosphere, the troposphere, ozone can damage human health, crops and ecosystems. It is also a greenhouse gas and contributes to global warming.

In a global assessment of the impact of ozone on climate change, scientists at NASA's Goddard Institute for Space Studies in New York evaluated how ozone in the lowest part of the atmosphere has contributed to temperature change over the past hundred years. Using the best available estimates of global emissions of gases that lead to increased ozone levels, the scientists' computer model revealed that tropospheric ozone was responsible for one-third to one-half of the observed warming in the Arctic during winter and spring (NASA, 2006).

In the Northern Hemisphere, ozone levels in the troposphere have increased by 35% over the past century, damaging forest and agricultural productivity, even when productivity has been stimulated by increased carbon dioxide levels. As well as reducing productivity, increased tropospheric ozone levels could alter the terrestrial carbon cycling by lowering the quantity and quality of carbon inputs into plants and soils (Loya et al., 2003).

On the other hand, global warming is reported to stimulate the production of the chemical precursors involved in ozone-generating photochemical reactions, contributing to the rise in ozone levels and indirectly stimulating further climate warming (Natural Resources Defense Council, 2004).

Agriculture is also central to any discussion of climate change. Not only is agriculture likely to be one of the victims of climate change, it is also a contributor to it by increasing greenhouse gas emissions. But agriculture also has great potential to contribute substantially to climate-change mitigation (Food and Agriculture Organization, 2008).

Ozone as an air pollutant

Ozone in the stratosphere forms a protective layer around the Earth that absorbs harmful ultraviolet UV-B radiation. Ozone is produced in the troposphere when its chemical precursors, such as nitrogen oxides, carbon monoxide and volatile organic compounds such as xylene, react in the presence of heat, sunlight and UV radiation (Natural Resources Defense Council, 2004). This surface ozone is a secondary pollutant and a constituent of smog.

The precursors of ozone are emitted in the atmosphere by a variety of natural and anthropogenic (man-made) sources**.** Natural sources of nitrogen oxides include microbial activities in the soil and lightning, and some enter the troposphere from the stratosphere. Nitrogen oxides are also produced by anthropogenic means, such as the combustion of fossil fuels by cars, power plants and other industries (Sadanaga et al., 2008). Volatile organic compounds such as isoprene and monoterpenes are produced naturally by natural forests and vegetation (Atkinson and Arey, 2003), especially by oak, maple, citrus, hickory, spruce, fir, eucalyptus and pine. Anthropogenic sources include the combustion of fossil fuel, petroleum refining, surface coating and the use of solvents (Choi and Ehrman, 2004). When injected into the troposphere, these compounds are oxidized and can produce ozone as a secondary trace gas.

In the Northern Hemisphere, ozone levels in the troposphere have increased by 35% over the past century as a result of industrial activity

and the rise in transport use. At the global scale, ozone has a significant greenhouse effect. At the subcontinental scale, close to inhabited areas, ozone affects air quality through smog and is responsible for both human health problems and vegetation damage.

The causes of global warming

Greenhouse effects

The Earth is heated by the sun. Solar radiation passes through the atmosphere and is absorbed at the Earth's surface (with a small portion being reflected back into space). This heat is lost from the surface as infrared radiation, but it cannot escape the atmosphere as easily as the solar radiation can enter. Instead, some of it is trapped by various gases that act in a similar way to the glass in a greenhouse—heat is allowed in but cannot get out—hence the term 'greenhouse gases'. This is fortunate, on the whole, because without this natural greenhouse effect the Earth would be at least 30°C cooler and life as we know it would not be exist (West Wales ECO Centre, 2004). However, it is now causing global temperatures to rise dangerously.

Greenhouse gases

The major greenhouse gases are water vapour, carbon dioxide, methane, nitrous oxide, chlorofluorocarbons (CFCs and their replacements) and ozone. Some of these occur naturally, some result only from human activity, and others occur both naturally and anthropogenically (West Wales ECO Center, 2004). The contribution of each gas to the greenhouse effect is a function of three factors: its atmospheric life-time, global warming potential and atmospheric concentration.

The rise in temperature

Recent human activities are increasing the natural greenhouse effect. The concentrations of certain greenhouse gases in the atmosphere are rising, so more of the infrared radiation emitted from the Earth's surface is being trapped. The planet is losing less heat and we are beginning to experience

global warming. Recent reports imply that the Earth's temperature and the level of carbon dioxide rise and fall roughly together, but it is not yet proven whether this is cause and effect triggered by either variable. Mankind's contribution is estimated to be 3% of the total increase in carbon dioxide.

Climate forcing

The Intergovernmental Panel on Climate Change (IPCC) concluded in its 2007 assessment report that increases in man-made greenhouse gas concentrations have 'very likely' caused most of the overall increase in global average temperatures since the mid–20th century.

Despite the widely accepted idea that carbon dioxide is the only driver of climate change (climate forcing) to be concerned about, scientists at the NASA Goddard Institute for Space Studies and the Colombia University Earth Institute have shown that air pollutants that damage human health and agricultural productivity, such as tropospheric ozone and black soot (particulates), also affect the climate (Hansen et al., 2000).

According to Hansen and Sato (2007), CH_4, N_2O, tropospheric ozone and soot (defined as black carbon and produced in the incomplete combustion of fossil fuels) together cause a forcing at least comparable to that of carbon dioxide (Figure 1). Ozone and its precursor methane clearly play a role in global climate forcing. The benefits of reducing these

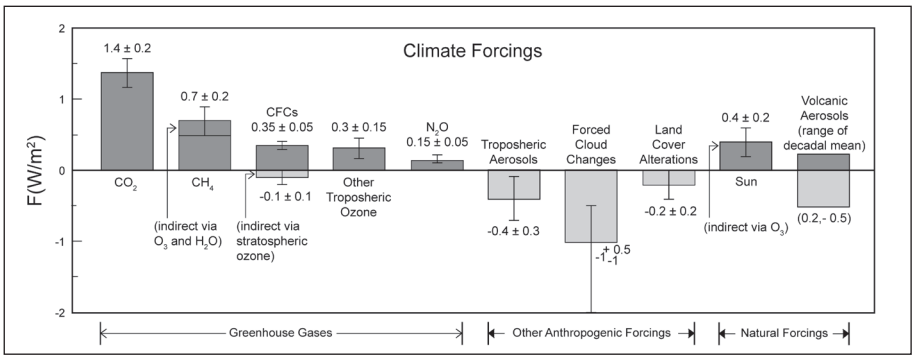

Figure 1 Estimates of climate forcing between 1850 and 2000.
Source: Hansen and Sato, 2007.

pollutants become more compelling as concern about global warming increases.

The IPCC's 4th assessment report in 2007 used the Hadley prediction chart (Figure 2) from the Climatic Research Unit at the University of East Anglia, UK, to forecast how the climate would change this century. According to their observations, average global temperatures are now 0.75°C warmer than they were 100 years ago. Since the mid-1970s, the increase in temperature has averaged more than 0.15°C per decade. This rate of change is very unusual in the context of past changes and is much more rapid than the warming at the end of the last ice age.

The IPCC predicts that surface temperature will rise between 1.4°C and 5.8°C during the period 1990–2100 (Intergovernmental Panel on Climate Change, 2007). The sea level will rise between 0.09 m and 0.88 m during the same period, depending on emissions; carbon dioxide (the most important greenhouse gas) has already risen from 280 p.p.m. to 379 p.p.m. since pre-industrial times, and its increase seems to be accelerating.

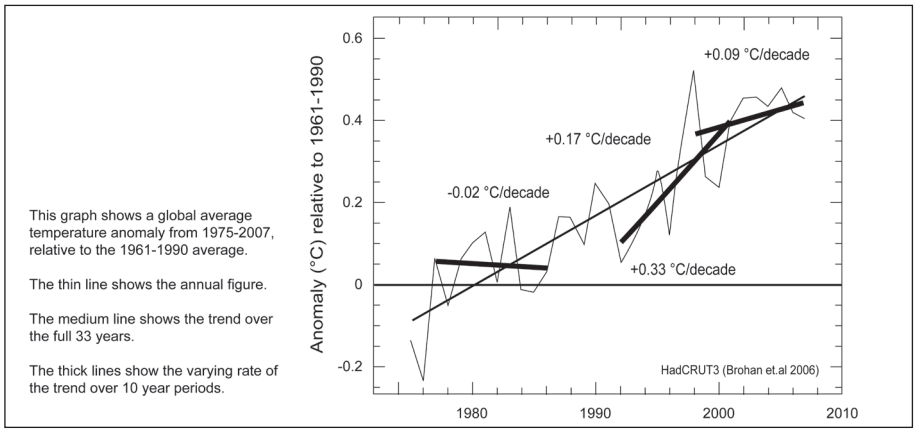

Figure 2 Average temperature anomaly from 1975 to 2007.
Source: Brohan et al., 2006.

Effects of surface ozone on plant productivity

Global warming and the concomitant carbon dioxide increase were expected to stimulate plant growth, but instead it seems that the tropospheric ozone is reducing plant growth by a considerable amount. According to recent

studies, the ozone is reducing plants' capacity to absorb greenhouse gases such as carbon dioxide. This means that ozone could be twice as important as we previously thought as a driver of climate change.

Ozone seems to affect plants' photosynthetic potential. It enters plants through pores in the leaves, called stomata. High levels of both carbon dioxide and ozone cause the stomata to close, so plants take up less of the carbon dioxide they need for photosynthesis and they produce less biomass. This interferes with photosynthesis, reducing their efficiency and leaving the plants weakened and undersized (Krupa, 2003), so they are less likely to act as a 'carbon sink' to soak up excess carbon dioxide from the atmosphere (Hopkin, 2007).

In addition, ozone affects carbon sequestration by the land biosphere. A study to determine the effects of increasing atmospheric carbon dioxide concentrations and tropospheric ozone levels on carbon allocation, cycling, sequestration, storage and biomass accumulation in boreal forest found that exposure to high levels of carbon dioxide and ozone together resulted in a marked decrease in above and below–ground tree growth (Percy, 2003). There was a 50% decrease in the formation rates of total and acid-insoluble soil carbon in forests when they were exposed to increased levels of both carbon dioxide and ozone.

Ozone also decreases the yield and productivity of crops, pasture, forests and ecosystems (Piikki et al., 2008; Reilly et al., 2007). More optimistic predictions of the effects of global warming on agriculture suggest that rising temperature and carbon dioxide levels could increase food production through longer growing seasons, higher temperatures, more active photosynthesis and an increase in crop yields, but this ignores the potential damage caused to agricultural crops by air pollution (Figure 3).

Effects of global warming on ozone levels

Ozone smog is sensitive to temperature, which is why the smoggiest days are always hot days in summer. Despite efforts to control air pollution, global warming is projected to reduce or even eliminate a lot of the efforts to control smog, and it may make ozone pollution worse. According to

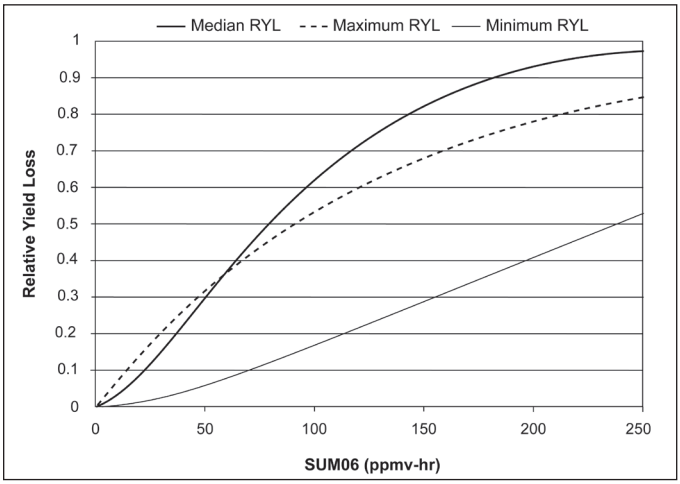

Figure 3 Relationship between relative percentage yield loss (RYL) and ozone exposure levels.
Source: Tong et al., 2007.

Stockwell (2004), if the climate becomes warmer and more variable, air quality is likely to be affected for several reasons:

- Warming influences the dispersal and ambient concentrations of many pollutants including ozone
- Higher temperatures stimulate chemical and photochemical reactions in the atmosphere that generate ozone, especially at temperatures above 32ºC
- Woody plants in particular emit biogenic volatile organic compounds called isoprenes, which are ozone precursors. These emissions are so temperature sensitive that an increase of as little as 2ºC could cause a 25% increase in emissions and a subsequent rise in ozone formation
- Rising temperatures also increase the activity of soil microorganisms, leading to increased emissions of nitrogen oxides, which are also precursors of ozone

Temperature increases could therefore raise ozone levels by increasing the concentration of ozone precursors. Researchers assessed how much ozone-dependent smog levels could rise over the eastern United States because of global warming. Their findings (Natural Resources Defense Council, 2004) are shown in Figure 4.

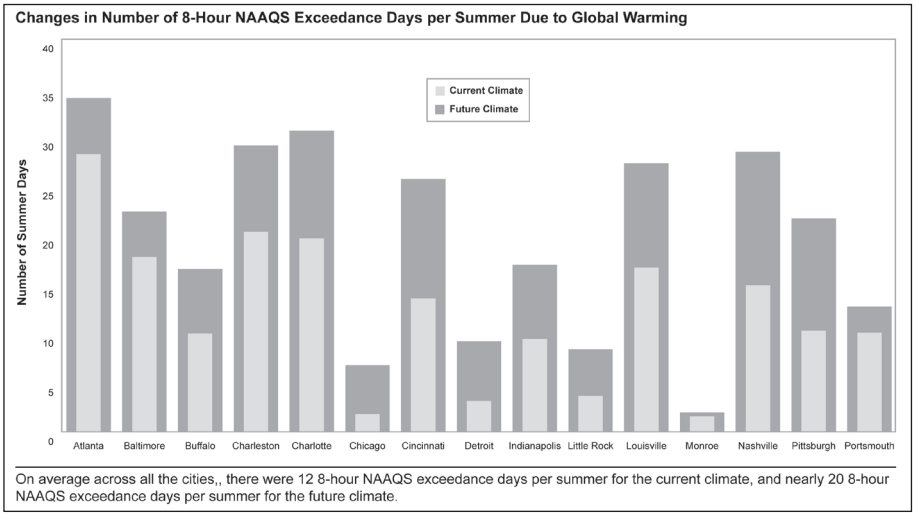

Figure 4 Expected rise in the number of days that fail to meet the National Ambient Air Quality Standards (NAAQS) in the eastern United States as ozone concentration increases.
Source: Natural Resources Defense Council, 2004.

Conclusions

Agricultural productivity is likely to decrease because of high temperature, droughts, floods and soil degradation caused by global warming. This will threaten the food security of many countries. Ozone-dependent yield losses and reduction of agricultural productivity may have an added detrimental effect on the food supply, especially as global warming will drive up the ambient ozone level.

Agriculture is likely to be one of the victims of climate change, but it is also contributes to climate change through greenhouse gas emissions. Even so, agriculture also has potential to contribute to climate-change mitigation. Carbon dioxide is consumed by plants and trees (known as carbon sinks) as they grow, so reversing deforestation and implementing reforestation programs can reduce atmospheric levels of these gases.

Measures to control the emission of greenhouse gases must take priority. Greenhouse gases can be cut by reducing the use of fossil fuels, cutting back on car use, investing in energy efficiency, implementing energy conservation measures, and switching to renewable resources such

as wind, solar and hydropower. Cutting fossil-fuel use will also have the benefit of reducing emissions of methane, nitrous oxide and ozone. The most important action is limiting coal use by restricting the building of new coal-fired power stations without carbon dioxide capture, and enforcing the installation of carbon capture technology in existing power stations. A gradual raise in the price on carbon emissions, in the form of a tax for example, will help to restrict the use of fossil fuels.

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Deserts: the new Powerhouses for Energy and Water

Hani El Nokraschy

Every country in the Middle East and North Africa (MENA) has an outstanding potential for solar energy. Concentrating Solar thermal Power (CSP) plants can be used to power the desalination of seawater, either by generating electricity or in combination with process steam, solving the problem of water scarcity in these countries. The AQUA-CSP study commissioned by the German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) and conducted by the German AeroSpace Center (DLR) quantified the potential of this technology in MENA countries and revealed the socio-economic and environmental effects of its widespread use. It has thereby provided a reliable database for decision-makers and policymakers in the water sector, and led to countries including this approach in their plans.

The growth of populations and economies, increasing urbanization and industrialization, and the limited natural resources of drinking water in MENA countries have led to serious shortages of fresh water. These countries need to establish a modern infrastructure for water distribution and improve the efficiency of water use and water management as soon as possible. However, they would still inevitably face considerable deficits, leading to the over-exploitation of groundwater resources. If they are to maintain a reasonable level of water supply, they have no choice but to desalinate seawater. However, basing the desalination of seawater on fossil

fuels is neither sustainable nor economically feasible in the long term, as fuels are increasingly becoming expensive and scarce. Concentrating Solar Power (CSP) offers a sustainable alternative to fossil fuels for the large-scale desalination of seawater. But the problem of water shortages is already pressing and MENA countries need to introduce CSP without delay.

Introduction

Freshwater sources in the Middle East and North Africa (MENA) are persistently over-used. This is partly due to the low efficiency of water distribution and use in these countries. Another reason is the continuous growth of populations and economies in this region, as more water is needed for more people and for new cultural, economic and industrial activities. In the past decade, the exploitation of fresh water in this region has exceeded the available renewable surface and groundwater sources, and leading to the over-exploitation of groundwater resources (Saghir et al., 2000). The provision of sufficient water is dependent on improving the efficiency of water management, distribution and use, although a pre-requisite for water management is having enough water to manage. Improved water management can delay and hopefully avoid the premature depletion of groundwater resources, but it cannot supply new, growing demands. That will require an increased supply of fresh water, but from where?

Possible solutions to the problem range from the transport of fresh water to MENA countries by tanker ship to the desalination of seawater (El-Nashar, 2000; Gasson and Allison, 2004). But all these solutions require significant amounts of energy. The sustainable supply of water therefore requires a sustainable source of energy, sustainable in this context meaning affordable, compatible with society and the environment, and secure. The prices of fossil fuels such as oil or gas have increased by 300% since the year 2000, and there are serious concerns about their effect on the global climate from carbon emissions. In addition, there are increasing conflicts about energy sources all over the globe, so it is obvious that the conventional energy system is not compatible with the requirements of a sustainable, secure and competitive supply of fresh water. As a result,

MENA governments are reluctant to invest in any of these solutions, but are instead putting increasing pressure on their groundwater. This is only a temporary solution, however, and will have disastrous results when these resources are depleted.

In pursuing solutions to energy shortages that seemed cheap and relied on proven technology, MENA governments have favoured solutions that are ultimately expensive. They hoped that investments in off-the-shelf technologies would guarantee a low-risk energy supply, but they were wrong. If such a situation is problematic in the energy sector, it is totally unacceptable in the water sector, as water is a vital commodity. Building a water supply on conventional energy sources could lead to a critical situation in the medium and long term. A different approach is urgently needed, aiming at a sustainable supply of both energy and water.

Concentrating Solar Power

The desire for 'least cost and proven technology' has prevented MENA governments from using a clean, unlimited and economic source of energy that is available on their doorstep: solar energy irradiated on the deserts and coasts (Figure 1).

Each square kilometre of land in MENA receives every year an amount of solar energy that is equivalent to 1.5 million barrels of crude oil. The

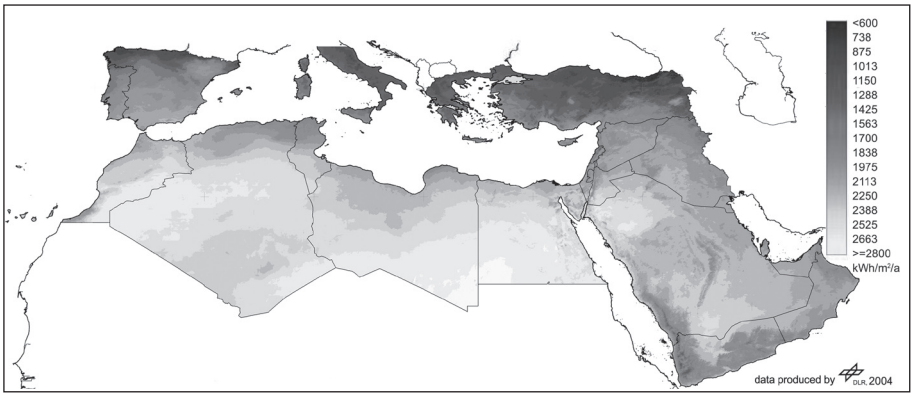

Figure 1 Annual direct solar irradiance in MENA countries and southern Europe. Pale colours indicate high irradiance.

technology to harvest, store and convert it to useful energy relies on concentrating solar power (CSP). A CSP plant the size of Lake Nasser in Egypt (the site of the Aswan Dam) would harvest an amount of energy equivalent to the present Middle East oil production. The solar energy received on each square kilometre of desert land is sufficient to desalinate 165,000 cubic metres of water every day.

Large fields of mirrors concentrate the sunlight to produce high-temperature steam for power generation or for the combined generation of electricity and heat; either way, energy is generated for the desalination of seawater (Figure 2). Part of the harvesteMixed-matrix membranes are hybrid membranes that consist of nanoparticles imbedded into a polymeric matrix. The nanoparticles, often made of a microporous material, allow much higher selectivity without compromising the flux. Various strategies are being investigated using a range of different nanomaterials, including zeolites, carbon molecular sieves, porous particles and even non-porous fillers. The selectivity is dependent on the free volume in the polymeric matrix, the size and surface features of the nanoparticles and the presence of covalent bonding, for exampled solar thermal energy can be stored for the night, and conventional fuel or biomass can be used as complement to guarantee round-the-clock operation. Heat from concentrating solar

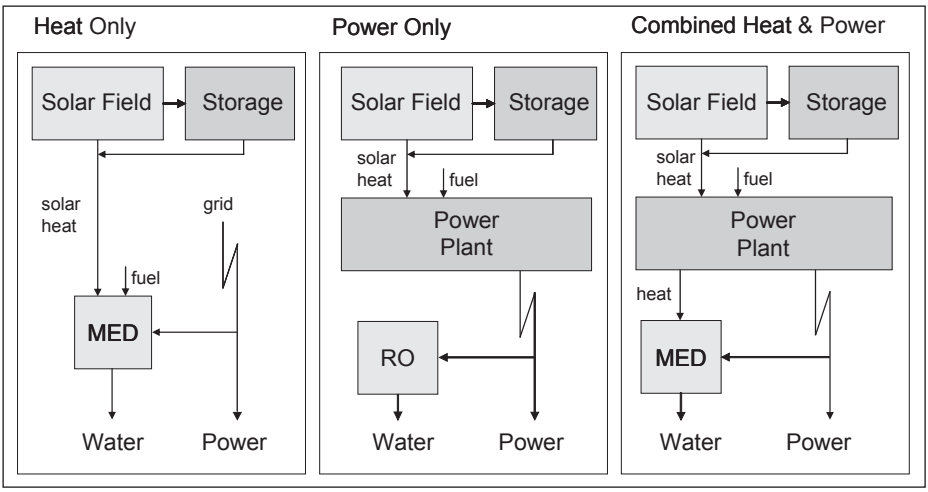

Figure 2 Left: Generation of heat for multi-effect desalination (MED). Middle: Power generation for reverse osmosis (RO) and other uses. Right: Combined heat and power for multi-effect desalination and other uses.

collectors currently has a cost equivalent to about US$50 per barrel of fuel oil, with a cost reduction of 50% likely in the coming decade thanks to economies of scale, mass production and technological progress, and this could fall to as low as US$15 per barrel by the middle of the century. This represents a great advantage over fossil fuels.

Concentrating solar power plants with unit capacities of up to 80 MW are presently in operation in the United States and under construction in Spain. The coastal CSP potential in MENA countries amounts to 5,700 TWh/y, with a total potential of 630,000 TWh/y (Trieb et al., 2005); at the end of 2008, the total global capacity of CSP had reached 510 MW/y. The engineering of a first plant for the combined generation of electricity, district cooling and desalinated water has started in Aqaba, Jordan (Trieb et al., 2007a).

Increasing demand for water

The growth rate of the population is one of the major driving forces for the rise in demand for fresh water. The population growth scenario used here is based on the intermediate World Population Prospects (United Nations, 2004). According to that study, the population in the total MENA region will steadily grow from about 300 million today to around 600 million by 2050 (Figure 3).

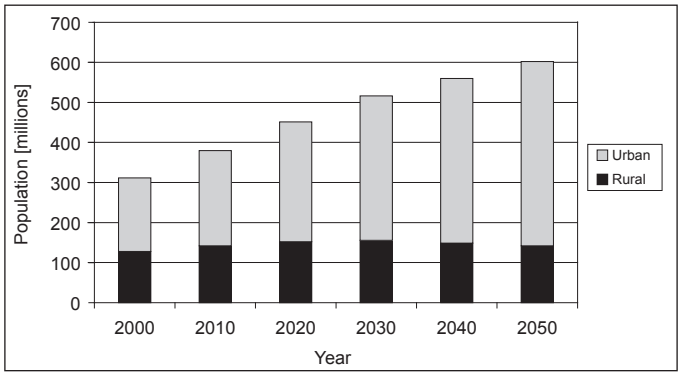

Figure 3 Expected population of the analysed countries in MENA according to a medium-growth scenario (United Nations, 2004).

The second driving force is economic growth, which can be assessed by the change in Gross Domestic Product (GDP). Long-term average growth rates for different countries have been selected in a range of reasonable values, with most countries achieving a per capita income similar to that of present Central European countries by 2050 (Trieb et al., 2005).

Calculations of the water demand for irrigation have been based on the population growth rate of each country. This implies that the present per capita water consumption for irrigation will be maintained, along with today's level of per capita food production in each country. Efficiency gains lead to a closing of 65% of the gap between present and best-practice irrigation efficiency (70%) for all MENA countries until 2050. The model also assumes a 65% closing of the gap between present water distribution efficiency and best practice (85%) until 2050. The general end-use efficiency is assumed to increase by 1.8% per year, leading to a general reduction in water consumption for constant water services of 60% until 2050. A similar development has been experienced in Australia over the past 40 years (Australian Bureau of Statistics, 2006), for example.

The resulting model of the development of freshwater demand in each country is shown in Figure 4. The demand for fresh water in MENA will

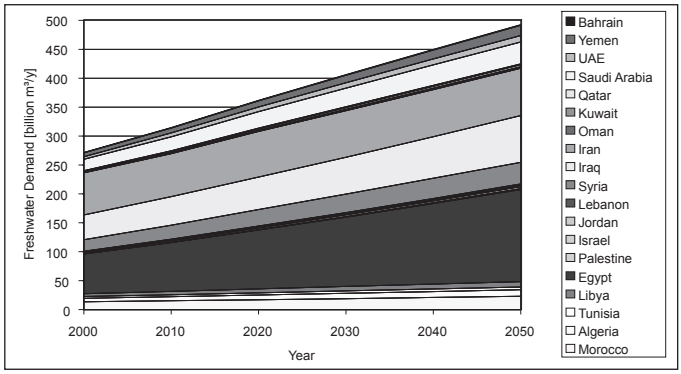

Figure 4 Freshwater demand estimated from the growth of both populations and economies.

grow more or less proportional to the population; the additional growth of per capita GDP and the related additional water services appear to be compensated by efficiency improvements. This demonstrates the crucial importance of water management, efficient distribution and end

use. However, it also shows that these measures alone will not be enough to cover the future demand of the MENA region, especially if present demand is already over-using natural groundwater resources.

Renewable Sources of Freshwater

Our analysis of the resources of fresh water is based largely on data from the AQUASTAT Database of the Food and Agriculture Organization of the United Nations, available at http://www.fao.org/ag/agl/aglw/aquastat/dbase/index.stm. The following definitions have been used for the water balances:

- Renewable water = Renewable surface water + Renewable groundwater – Overlap
- Exploitable water = Renewable water × Exploitable share
- Sustainable water = Exploitable water + Reused waste water
- Water demand = Agricultural demand + Municipal demand + Industrial demand
- Deficit = Water demand – Sustainable water
- Unsustainable Water = Deficit – CSP desalination = Fossil-fuel-based desalination + Excessive groundwater withdrawal

In our model, the amount of reused waste water increases continuously from the present statistical values of each country until it reaches a best-practice rate of 50% within the municipal and industrial sector in the year 2050. The sustainable water is shown in Figure 5 along with the agricultural, municipal and industrial freshwater demand of the MENA region. Sustainable water increases with time thanks to presently untapped resources in some countries that will be exploited in the future and to the increased reuse of wastewater in the municipal and industrial sector. The difference between sustainable sources and water demand leads to a water deficit.

There is already a significant deficit today, which is covered by seawater desalination based on fossil fuels and by the over-exploitation of groundwater resources. As a result, groundwater levels are falling, salt water is intruding into groundwater reservoirs, and many regions in MENA are undergoing desertification. According to our analysis, this deficit will increase from 50 billion MWh per year, which is almost equivalent to the annual flow of the River Nile to Egypt, to 150 billion

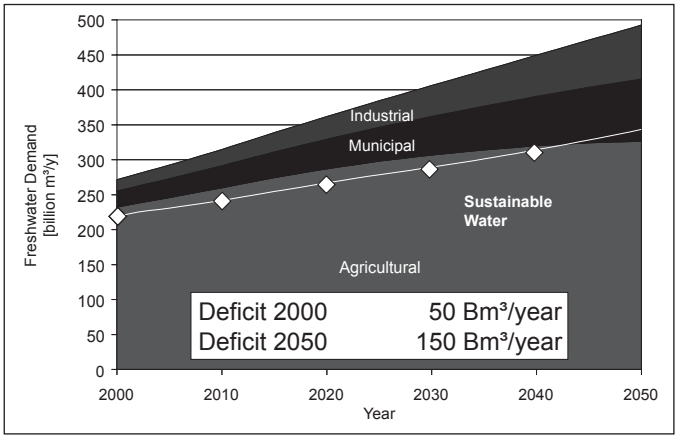

Figure 5 Industrial, municipal and agricultural freshwater demand in MENA are shown in comparison with the sustainable freshwater resources of the region (white line). The increase in sustainable water is due to the increased re-use of water and to resources in some countries remaining presently untapped.

MWh per year by 2050. Egypt, Saudi Arabia, Yemen and Syria are the countries with the largest future deficits. Increasing efficiency of water distribution, use and management to best-practice standards is already included in the underlying assumptions of this scenario. It is obvious that MENA countries will face a serious problem in the medium term if these standards are not implemented and additional measures are not initiated very soon. These additional measures should include concentrating solar power technology for seawater desalination.

Using solar power for desalination

Both water and energy are available in abundance in MENA, in the form of seawater, solar radiation and other renewable energy sources. Future water and energy deficits could be covered by solar thermal power plants, used in conjunction with thermal multi-effect desalination, and by using solar electricity for reverse osmosis. Other renewable sources of heat and electricity will also be used for these purposes. We have not distinguished the individual potentials of the different technologies for desalination,

only their potential as a whole, and we have assumed that CSP would cover it all, as it has the largest potential for renewable energy in the region (Trieb et al., 2005).

From 2020 to 2030, the growing freshwater deficit could be increasingly covered by desalination plants powered by renewable energy, mainly CSP, reducing the non-sustainable water supply, and providing most of the non-conventional water by the year 2030 (Figure 6). Until 2030, the increasing deficits will have to be bridged by fossil-fuel-powered desalination and the removal of groundwater, in the hope that those resources will remain available and affordable until then. This may seem optimistic, but there are

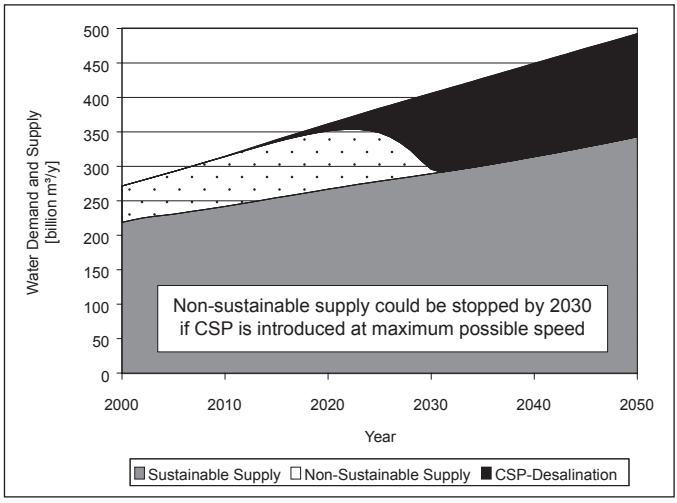

Figure 6 Water demand in MENA until 2050 and coverage by sustainable sources, unsustainable sources and solar energy (CSP desalination).

no sustainable and affordable alternatives. It is reassuring that the potential of CSP is not limited by either the availability of solar energy or its cost. Indeed, the only limit on CSP is the speed of CSP capacity expansion.

However, a considerable increase in the non-sustainable use of water will occur in the meantime, reaching a peak between 2015 and 2025 (Figure 7). This calls for great improvements in freshwater management and the efficiency of its use in both urban and rural regions if MENA countries are to have a satisfactory and sustainable water supply. Seawater desalination using renewable energy is not an alternative; it can only

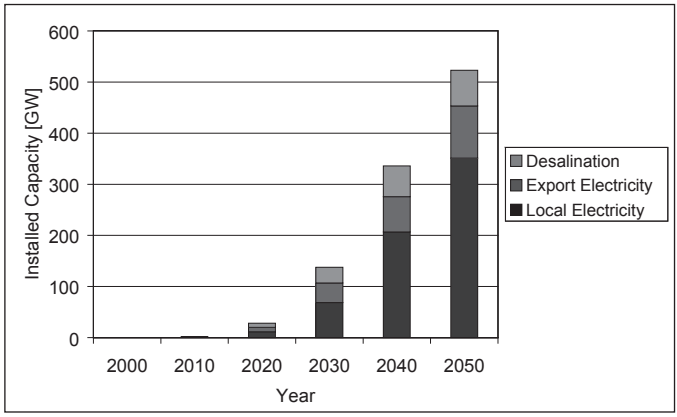

Figure 7 Scenario of market expansion of CSP resulting from different studies for the local supply of electricity in Europe and MENA, for export of solar electricity from MENA to Europe, and for seawater desalination in Europe. Data from Trieb et al., (2005, 2006, 2007b).

complement other measures. The measures recommended by the Food and Agriculture Organization (2002) include:

- Increasing irrigation efficiency (from less than 40% now to 70%)
- Increasing the efficiency of municipal water distribution (from less than 50% now to 85%)
- Increasing the general efficiency of all end users of water by at least 1.5% per year
- Avoiding upstream soil erosion resulting from excessive logging and other activities
- Concentrating agriculture on high-value crops with low water demands
- Avoiding the overexploitation of groundwater resources, because this will cause the groundwater level to sink and favours the intrusion of salt water
- Cleaning and reusing at least 50% of municipal and industrial wastewater
- Harvesting rain water in small-scale distributed basins and dams

Neglecting these measures would lead to a much higher deficit than that shown in Figure 6. A sustainable supply can only be achieved in time if they are made a high priority (Gleick, 2004; Schenkeveld et al., 2004). To quantify the CSP potential for desalination, we have assumed in our model that all plants will be combined with multi-effect desalination, and all the electricity generated is used for reverse osmosis. Given the rapid increase in water deficits in MENA, this may be necessary to avoid a

severe overexploitation of unsustainable water sources. This model leads to a minimum installed (electric) capacity of CSP needed to cover future water deficits in MENA and to the maximum possible speed of expansion of this technology.

In MENA, the capacity of CSP plants until 2050—if they are installed exclusively for seawater desalination—would amount to a total of 65 GW. North Africa (32 GW) has the largest potential for CSP desalination plants, followed by the Arabian Peninsula (25 GW) and the Western Asian countries (8 GW).

CSP production of 115 TWh per year in 2025 and 550 Twh per year in 2050 may be used for desalination purposes. This will require 10% of the existing coastal CSP potential. After 2030, the CSP desalination capacity will be large enough to cope with the freshwater demand and less solar desalination will be needed.

Water desalination and power generation

Obtaining sustainable supplies of water and energy are closely related challenges for the MENA region. If seawater desalination is a viable option to escape the threat of a water crisis, a sustainable source of energy will be required to power it. At the same time, the energy demand in MENA is growing rapidly, and a sustainable solution must be found for energy too. In the past decades, fossil fuels from MENA have been the motor of the economic development in today's industrialized countries. But just when MENA countries are starting to boost their economies too, those resources are now becoming scarce, threatening climate stability and depriving MENA from securing its own economic development.

However, MENA countries have access to several different renewable energy sources, such as wind power, hydropower, biomass and geothermal energy, and solar energy, which on its own has the potential to exceed the world's total energy demand by several orders of magnitude. Less than 1% of the land area would be required to power MENA in a sustainable way and to provide enough electricity for export to Europe to supply 15% of its demand by 2050 (Trieb et al., 2006).

Underlying a scenario for the expansion of CSP technology in MENA (Figure 8), the cost of concentrating solar collector technology will

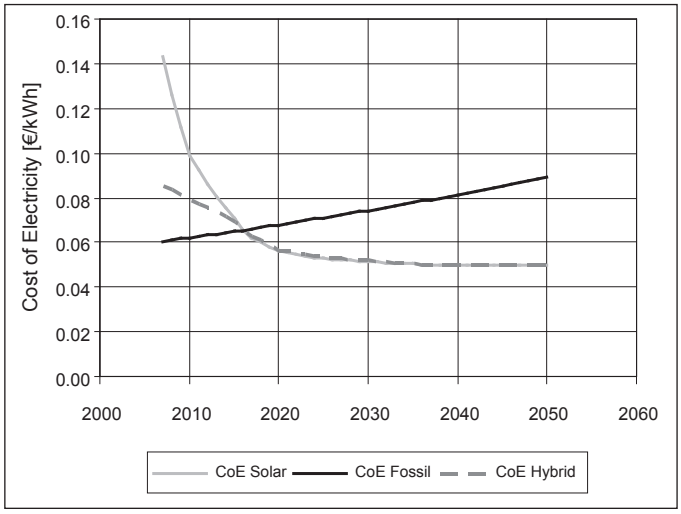

Figure 8 Cost of electricity from CSP plants compared with gas-fired (fossil fuel) and hybrid power stations, assuming a 5% project rate of return, 25 years of life, a fuel cost of 25 US$/MWh fuel cost, a 1%per year escalation rate and irradiance of 2,400 kWh/m²/y.

come down from around 300 US$/m² to about 150 US$/m² by 2015 and 100–120 US$/m² by the middle of the century (Trieb et al., 2005). But considering also the introduction of thermal energy storage and the option of prolonging solar operation to base load, solar electricity costs from CSP in the long term will be as low as 0.04–0.06 US$ per kWh, depending on the solar irradiance of the site (Figure 9). This will compare very favourably with electricity from fossil fuels, as combined cycle power stations using natural gas have an unsubsidised cost of about 0.06 US$ per kWh with an increasing trend.

CSP plants that produce both power and water can sell electricity at a competitive price and at the same time deliver water at the price shown in Figure 10. Shortly after 2015, water from CSP desalination will be considerably cheaper than water from conventional desalination powered by conventional fuels. In the medium term, it can achieve a price of less

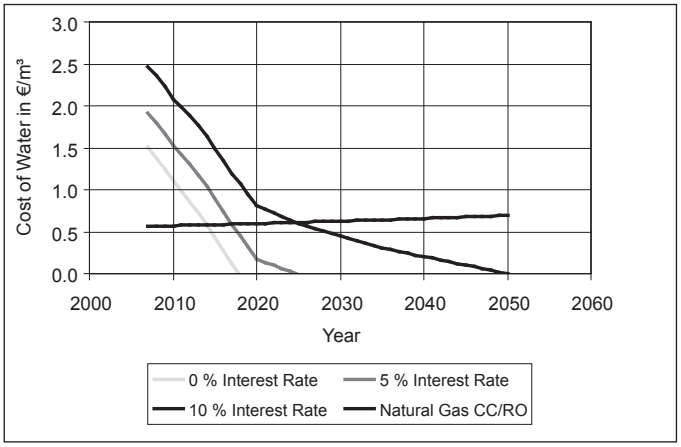

Figure 9 Cost of seawater desalinated by CSP in co-generation with multi-effect desalination according to Figure 3 (right) for a 0%, 5% and 10% project rate of return, assumed revenue for electricity, 7,500 full load hours per year, annual irradiance of 2400 kWh/m²/y. Data are from Trieb et al., (2007b).

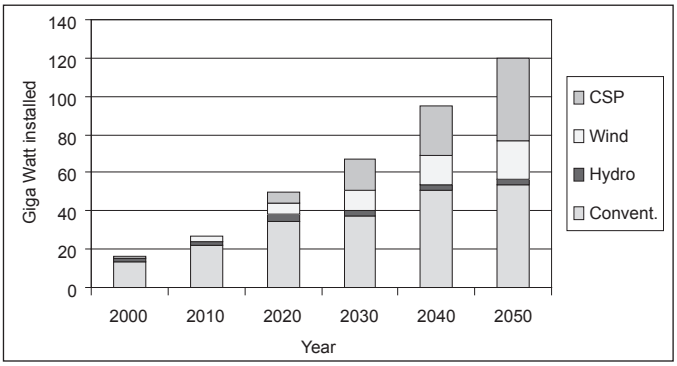

Figure 10 A scenario for the gradual but immediate transition to renewable energy in Egypt.

than 0.10 US$/m³, which would be competitive even for irrigation. Until then, a series of pilot and demonstration plants of a total of 5,000 MW capacity must be installed worldwide to achieve the necessary economies of scale and cost reductions. MENA countries can participate significantly in this task, with major benefits for the region.

Time for action in MENA

The MENA region is facing a water crisis on a scale that has never been seen before. But building a sustainable alternative will take a considerable time. That is why the governments of MENA countries should act immediately to establish the political and technological conditions needed for efficient water management and for the rapid introduction and expansion of CSP and other renewable energy sources for power and seawater desalination.

Seawater desalination based on CSP offers enough affordable, sustainable and secure freshwater to cope with the growing deficits in the MENA region. In fact, it is difficult to envisage any viable alternative to CSP.

Starting with zero installed capacity in 2008, it will take at least 10–15 years until the CSP production capacity will be large enough to cope with the quickly growing water demand of the region. Even with the fastest possible introduction and the full implementation of efficiency measures, the unsustainable exploitation of groundwater cannot be ended before 2030. Even this is rather optimistic. However, a change to a sustainable supply is possible at least until the middle of the century if the necessary measures are initiated now. There is no time to waste.

The challenge facing Egypt

As a MENA country, Egypt faces the threat outlined above, and should respond immediately by shifting to renewable energy for its electricity supply. This is the first step towards sustainable seawater desalination.

The rapidly increasing demand for electricity in Egypt and the abundant resources of renewable energy—notably hydropower, wind energy and solar irradiance—maker renewables the only logical choice. A complete shift to renewables is possible because of the excellent potential of CSP, which allows electricity generation in the night and on demand by means of hybrid operation or heat storage. However, such a shift will take time. Even assuming that all new power plants built use renewables, this will not satisfy the demand, which is growing at a rate of about 7% per year.

In the first decade, hydropower will be used, as it is already being planned. In the first and second decades, wind power will be used increasingly

to provide about 15–20% of the installed capacity in the Egyptian grid (Figure 10).

In the following decades, CSP plants must be built on a large scale to replace thermal power stations that go out of service and to cover the domestic demand, especially the growing demand for desalination, and to have a surplus of electricity for export to Europe. This can be the start of a large-scale Mediterranean Renewable Energy Partnership.

There are concerns that a high percentage of wind energy might destabilise the grid, but Egypt can get round this by limiting its share to 15–20% and installing extra capacity in the form of conventional power stations and CSP with thermal storage to enable night operation and supply on demand.

After 2050, the share of conventional power stations can be reduced by replacing them with CSP power stations, which will be able to produce electricity at much lower costs than can be achieved using oil and gas today.

The year of German-Egyptian Science and Technology in 2007 offered an excellent opportunity to lay the basis for future cooperation between German and Egyptian scientists. They were able to establish a framework for shifting electricity generation in Egypt to 100% renewables during this century, and to enable electricity exchange with Europe within the Mediterranean Renewable Energy Partnership.

The mediterranean renewable energy partnership

Renewable energy resources are available all over the world with different intensities. However, they are not always abundant in the regions where energy is needed the most. The Mediterranean Renewable Energy Partnership means that renewable energy can be harvested where it is economic, with wind power from Northern Europe, the Gulf of Suez and Morocco's Atlantic coast, and solar power from North Africa and the Middle East. The energy can then transmitted to where it is needed most, in central Europe, just as oil and gas are transported there now. It is more cost-effective to proceed this way than for each country to try to produce renewable energy from local resources, which may be weak.

Solar thermal power stations offer the option of hybridisation and/or thermal storage. This will enable the production of electricity day and night, and on demand, just like conventional power stations. The option of seawater desalination increases their economical features.

The German Federal Minister for the Environment, Sigmar Gabriel, told the fourth Middle East–North Africa Renewable Energy Conference in Damascus:

> 'Solar energy offers huge potential, which is currently going all but unused. Studies on potential carried out by the German Aerospace Center conclude that solar thermal power plants in southern Europe and North Africa can make a significant contribution to sustainable energy supply in Europe.
>
> This vision is groundbreaking: it means that in 20 to 30 years we will be able to obtain some of our energy from solar thermal power plants.
>
> To achieve this we need adaptation of the political framework conditions in your countries and dismantling of subsidies for fossil energies; at the same time we need to strengthen regional cooperation and provide joint investments for the expansion of a stable electricity grid. An electricity grid that crosses borders and the Mediterranean poses no technical problems at all. There are already electricity grids between Spain and Morocco and hopefully there will soon be a first connection from Tunisia to Italy.
>
> However, to ensure that electricity, for example from solar thermal power plants, can be conducted to Central Europe in the coming 20 years, we need greater political will.'
>
> The whole speech is available here: http://www.menarec.org/MENAREC4.html.

Following the minister's recommendations, a political and financial framework is essential to govern the activities of such a huge project. In the early phase, European countries should provide strong support to MENA countries to accelerate its development. The target is for MENA countries to supply 10–15% of Europe's demand from clean electricity.

The Mediterranean ring, operating at 400 kV alternating current, is nearly complete. It can be considered as just the beginning of commercial electricity exchange between the connected countries, as it only has limited capacity and the losses for long-distance transmission are too high.

For these reasons, another transmission technology will be adopted: High Voltage Direct Current (HVDC). This will connect with high-performance lines, each one capable of transmitting 5 GW, from the renewable-energy collection centres in North Africa and the Middle East directly to Central Europe (Figure 11).

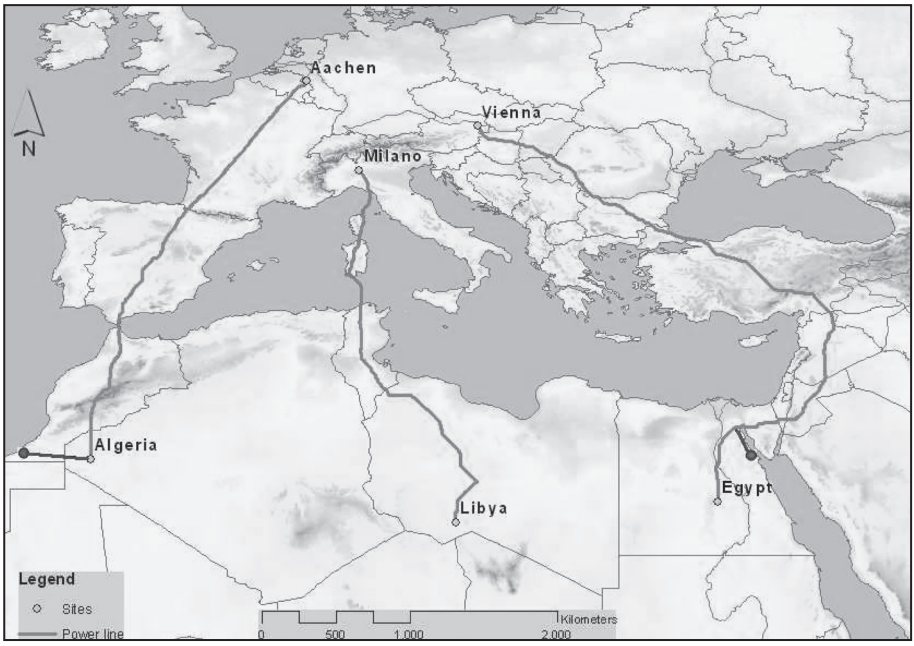

Figure 11 Three examples of HVDC lines connecting Europe with MENA. From Trieb et al., (2006).

How the partnership will work

The best way to explain the framework suggested here is to use the example of participation between Germany and Egypt. The first step is to establish a company in public–private partnership, with the participation of the German and the Egyptian governments, to construct and operate an HVDC transmission line from Egypt to Germany. A German private company will establish a joint venture with an Egyptian private company to create a wind field or a solar thermal power station in Egypt. We will consider the case of a solar thermal power station. The concept of a solar

hybrid station, which uses fossil fuel to generate power at night, is chosen to ensure supply on demand. The solar electricity share, totalling at least 20% of the power generated, will be transmitted to Germany while the conventional share will be used in Egypt. In addition to electricity, the plant will produce desalinated water from the waste heat of the power station, making the plant even more economical.

What can Egypt do?

Egypt can transfer the subsidies for fossil fuels to a subsidy for electricity at the user side, giving incentives for electricity generated from a renewable source. It can offer free land and infrastructure to give the project a boost. It can then buy the conventional electricity share (for example at 0.025 US$ per kWh) and buy the desalinated water produced (for example at 0.50 US$/m^3). It can then guarantee by law capital security and ensure that the project is free of taxes for the first ten years.

What can Germany do?

Germany can set a quota for clean electricity and increase it each year by 1% over the actual value for each electricity producer. This is compatible with the renewable-energy target of 20% set in 2020 by the European Commission and Germany. It can extend support to clean electricity for supplies from the HVDC lines from Egypt. It can set an incentive bonus for the import of clean electricity over the price of conventional electricity, for example €0.08 per kWh for solar electricity and €0.04 per kWh for wind electricity. It can give a priority feed-in to the German grid. The price bonus will be valid only for the clean share of a hybrid system and is guaranteed for 10 years, after which the bonus is reduced by 10% each year.

What can both countries do?

Egypt and Germany together can establish a public–private partnership to build and operate the transmission lines.

A 'Win–Win' situation

Germany benefits from:

- Clean and cheaper electricity

- Employment as the machinery must be made and exported
- Investing capital instead of spending it burning fossil fuels
- A diversification of energy supplies

Egypt benefits from:

- The desalination of large amounts of water
- The ability to sell electricity for a reasonable price.
- Social and economic development
- Employment and access to high technology

The environment benefits from:

- Less carbon dioxide emission
- The development of low-cost equipment and the extension of the solar share to 100% using heat storage

Conclusions

I have shown that it is possible, and even economically beneficial in the long term, to cover Egypt's needs for electricity and water from the technology of Concentrating Solar Power and other renewable energy sources. A favourable side effect is that the renewable energy available can cover all of Egypt's demands and provide a surplus for export to Europe in the framework of a Mediterranean Renewable Energy Partnership.

Acknowledgements

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From the Foreword by Ahmed Nazif, Prime Minister of Egypt

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