New Life Sciences:

FUTURE PROSPECTS

BioVisionAlexandria 2010

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

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BIBLIOTHECA ALEXANDRINA
مكتبة الإسكندرية

Bibliotheca Alexandrina Cataloging-in-Publication Data

BioVision Alexandria 2010 : Alexandria, Egypt)
New Life Sciences : future prospects : BioVisionAlexandria2010 / Bibliotheca Alexandrina ; editors, Ismail Serageldin, Ehsan Masood, with Mohamed El-Faham and Marwa El-Wakil. – Alexandria, Egypt: Bibliotheca Alexandrina, 2011.
p. cm.
Includes bibliographical references.
ISBN 978-977-452-149-8

1. Biotechnology -- Congresses. I. Serageldin, Ismail, 1944- II. Masood, Ehsan. III. El-Faham, Mohamed. IV. El-Wakil, Marwa. V. Aliksandrina (Library). VI.Title

660.6--dc22 2011593101

ISBN 978-977-452-149-8
Dar El Kotob Depository Number 4131/2010

E-mail: secretariat@bibalex.org
The information in this publication is solely the responsibility of the author.

Text design and layout: Cherine Bayoumi and cover design: Hany Saber

Printed in EGYPT

1000 copies

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Acknowledgements

We are grateful to all who have made the BioVisionAlexandria 2010 Conference the success it was. First and foremost, the Egyptian Government whose support of the Conference is highly appreciated.

Our deepest appreciation also goes to the distinguished Nobel Laureates, speakers, session chairs, discussants, rapporteurs and participants without whom this conference would not have been possible. A sincere thanks to our partners; The World Life Sciences Forum, BioVision who inspired us to take this road and have been a help and support ever since.

A special thank you to Mohamed El-Faham, Marwa El-Wakil, Omneya Darwish, Asmaa Soliman, Yasmin Maamoun, Esraa Ragab and the conference organizing team at the Bibliotheca Alexandrina who worked day and night to make this event a success. Also to Cherine Bayoumi for her creativity and super-efficient design and layout, Hany Saber for the cover design and Marian Roushdy and Lara El-Mallakh for data collection and for attending to every single detail of the proceedings preparation. Many thanks to Esraa Ragab, Riham Khattab, Shaimaa El-Fadaly, and Magdy Khalil, for proof-reading, Nevine Noreldin for the book citations and Olfat Gafour for her continuous support and guidance. In addition to all the staff at the Bibliotheca Alexandrina who contributed to the production of this volume specially Hanan Abdel Razek and Mohamed Gomaa.

The following organizations have in many different ways supported the Conference, to which we would like to express our sincerest gratitude

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Foreword

Hani Helal

The Prime Minister of Egypt, Dr. Ahmed Nazif wanted to be with you but due to previous commitments was unable to participate and delegated me to be with you today.

I have been with you in BioVisionAlexandria 2006. Unfortunately in 2008 I was unable to be with you and today in 2010, I am really honored and pleased to be here.

For me BioVisionAlexandria 2010 has a special flavor. First of all because 2010 is the year of Science and technology with France and BioVisionAlexandria is a partnership between BioVision Lyon and the Library and it adds to the partnership that the Library and Egypt is having with France. The second reason is that France, two days ago has donated the most important donation in history according to my knowledge to the Library of Alexandria. 500,000 books in all disciplines of knowledge have been donated by the BNF, the National Library of France to the Library. This is why BioVisionAlexandria 2010 for me is a special event and for Egypt as well.

Let me also on behalf of the Egyptian Government congratulate the organizers and BioVisionAlexandria and BioVision Lyon as well for giving this opportunity and platform for gathering eminent scientists, Nobel Laureates, decision makers, scientists, leaders from industry and society for such a forum in which there is a huge amount of information and dialogue and discussion and the most important thing for me is to explore how can we use science, especially the life sciences to face the challenges of today and tomorrow.

This platform is a good opportunity for North-South dialogue and cooperation. Also South-South dialogue and cooperation and most importantly the young scientists that we receive today at the Library because this is our focus even is Egypt.

Remember in 2006 when I give my speech I told you that we are going to reform science and technology in Egypt but I think now I can say that we have a very clear strategy for science and technology in Egypt. Egypt is going towards the knowledge-based economy. We have gone through a very successful reform in our economy and in spite of the international and financial economic crisis, Egypt has done so well till now to pass through this critical path but we do believe that in order to continue and complete our reform and economic growth, science and technology and knowledge are very important. Knowledge means education, research and innovation. This is why we have reformed our science and technology government system.

We established a science and technology higher council chaired by the Prime Minister, 8 leading ministers in the cabinet of ministers and 9 eminent scientists and leaders in the society including Ismail Serageldin, Ahmed Zewail and Adel El-Beltagy. This council will and is putting the priorities of science and technology strategy in Egypt. I think the priorities that have been identified are not different form all the priorities that you and other countries are talking about.

The second major reform in Egypt is establishing a new mechanism of funding and financing science and technology. We established a new science and technology fund to complete the cycle. I think you have talked about 4 Ps. 4 Ps for us means the complete cycle of science and technology; publications, patents, prototypes and products. This science and technology fund is doing very well and now everything is based on competitiveness and quality. Human Resource development is a major axe for the reform and we have a very ambitious plan for this human resources development.

Focusing on young scientist and this is why we are really happy that we have here today many young scientists. I would add on behalf of my ministry that Egypt would support the participation of 10 or 20 young scientist in BioVison.Nxt generation and it will be completely funded by the Ministry of Scientific Research.

One of the most important tracks is international cooperation and President Mubarak in December 2006 announced that the decade of Science and technology in Egypt, 10 years of working with milestones and indicators. The international cooperation is a major track. We invented a new mechanism of cooperation we called it science and technology year with different countries. In 2007 we started with Germany, 2008 with Japan. We are glad that Japan has agreed during this year to establish the first ever Japanese University for science and technology with Egypt outside Japan in Borg El-Arab. A center of excellence for science and technology not only for Egypt but for the region and for Africa. 2009 with Italy and 2010 with France and we will continue.

Ladies and gentlemen, dear colleagues, you are gathering here today to discuss very important issues. I think that there is a strong need for the new technologies and advances in science to address today's and tomorrow's needs. I think we have many questions raised in the society. There are many people outside this hall who are waiting to hear from you how can we use science and technology especially in life sciences to address and implement social goals. When you are talking sometimes about the economic reform people say we would like to feel the economic reform. People outside this hall would like to hear from you how they can benefit from your discussion and your research. How can we address the global issue of water and how can we manage it universally. How can we go for the green energy, sustainable development in agriculture. How can we deal with climate change, how would it affect coastal cities like Alexandria for example and what are the innovative ideas that would come from such a forum. How can we get healthcare access to all people, not only to rich people. How can we link research, development, innovation with industry and economic development.

I'm sure that you will deliberate all these questions and you will exchange views and experiences together. Most importantly is to give our young scientists, the new generation, the perspectives and the power to continue in this direction.

Last but not least you are going to deal with how the brain functions but as a political person now I would like that we deal also with the brain drain. I think that this is a crucial issue that we have been discussing all the time. Last March in Vienna during the Bologna Forum of Ministers of the European Commission and the Bologna delegation and 15 countries outside the European Commission. Egypt has proposed a new concept of brain circulation. We would like to adopt the Brain Circulation. The European Commission adopted the principle I think that such a forum is very important to discuss how we can keep the brains where they would serve their countries.

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FIRST WORDS

A Bio-Based Society for a Sustainable World

Philippe Desmarescaux

Many things have happened since the previous BioVisionAlexandria event in 2008, particular in three key areas:

First, we have seen fast-paced development of knowledge and technologies in the field of life sciences, opening up a wide range of opportunities for improvements in health care, agriculture and environmental protection, but at the same time creating in some cases new doubts and obstacles, and perhaps greater risks. Choosing the best solution is therefore fundamental and we must do so while taking into account all available expertise and addressing the concerns which are raised.

Second, we have seen more widespread awareness of the effects of greenhouse gases and climate change caused in large part by human activities. But this level of awareness was not sufficient to allow the international conference in Copenhagen in May 2009 to produce a structured plan of action with clear acceptance and commitments from all parties and in particular from the US, Europe, the BRIC countries and developing countries. This is all the more disappointing because we know that something must be done very soon to reverse the trend by implementing efficient actions.

And third, France has taken steps to overcome political divisions to discuss the best action plan to achieve concrete results through binding measures to drastically reduce CO2 emissions and to promote sustainable development: in France this round of consultations is known as the 'Grenelle initiative for the environment' which ended in November 2009.

The key outcomes are:

- Incentives for developing carbon neutral energy sources, in particular agro/biofuels
- Measures to stop the decline in biodiversity and protect all forms of life
- Wider use of ecologically productive agricultural practices
- More support for research in biotechnologies and GMOs in order to better understand their impact on the environment
- A new campaign to raise awareness on the issues of sustainable development and encourage action through education among young people and also in companies, local government agencies and the state
- These wide-ranging actions are necessary to change attitudes in France and to start experimenting new approaches on a much larger scale and to measure their effectiveness both from an ecological and economic perspective
- But the efforts made in France will have little effect on a global scale because France accounts for no more than 2 or 3% of worldwide emissions. Furthermore, if France is the only country to take such measures, it risks penalising its own national economy which would alone bear the cost of sustainable development

In this context, we here at BioVisionAlexandria can either lament the situation and wait for a global consensus to emerge in which countries will set their objectives in accordance with those of the international community; or we can help accelerate the process by expressing our strong convictions and by sharing suggestions and experiences which we find pertinent.

This is what Ismail Serageldin has encouraged us to do in the coming three days, in this legendary city, and I join with him in saying that once our presentations, discussions and conclusions have been published, they will have wide-reaching importance in achieving a better-preserved planet and a more responsible human community for the benefit of all, today and for future generations.

I am confident of this because the themes addressed at our forum are central to current concerns: be it finding the best alternatives for providing drinking water and food production sufficient to meet the needs of the soon 9 billion people of the world, be it the intelligent protection of biodiversity, or finding the least expensive and most efficient treatments to ensure good health for all.

To do this, we will have to optimize any and all synergies at the interface of life sciences, information technologies (ICT), nanotechnologies, as well as robotics. We must also develop clean technologies and geo-engineering: we have to completely rethink science and technology in order to serve the urgent needs of the planet.

I am also confident that the political commitment which proved elusive in Copenhagen will be far easier to achieve if the technical solutions are better understood and their economic impact better evaluated and optimized.

Also, the technical solutions will be all the more appreciated at the political level if they have been fully tested and validated by international teams of experts from both the northern and southern hemispheres: this is one of BioVisionAlexandria's great assets because it gathers leading thinkers from all corners of the globe and encourages not only open dialogue but also joint action. We here in Alexandria cannot settle for analyses and proposals: 'a vision without a plan is an illusion.'

In conclusion, if we hope to meet these many challenges in order to achieve a 'sustainable world,' we will have to accept new ways of life, adapted to the culture and social context of each country.

But above all, we will need to rely on scientific and technological progress: as Pope Benedict XVI wrote in his latest encyclical, 'The challenge of development today is closely linked to technological progress, with its astounding applications in the field of biology,' which reminds us of the words of the Prophet: 'The ink of the scholar is better than the blood of the martyr.' Benedict XVI added that, 'Development is impossible without upright men and women, without financiers and politicians whose consciences are finely attuned to the requirements of the common good.'

Seeking the common good will always require a rigorous analysis from an ethical standpoint of the various solutions proposed.

Then, with these new ways of life, new technologies, a widely shared concern for the common good and a rigorously ethical approach, we will indeed bring forth 'a bio-based society in a sustainable world.'

Science and Social Responsibility

Mohamed H. A. Hassan

BioVisionAlexandria places a well deserved spotlight on Bibliotheca Alexandrina, one of the world's great institutions of learning and culture. It also reflects the expanding scope of North-South cooperation in the new frontiers of the life sciences. TWAS, the Academy of Sciences for the Developing World, has been a proud partner of BioVisionAlexandria ever since the conference was launched in 1999.

The ties between TWAS, and Bibliotheca Alexandrina run deep. I fondly remember the Library's generosity in hosting TWAS's 16th General Meeting in 2005. More than 250 renowned scientists, scholars and policy makers from around the world attended the event. President Hosni Mubarak gave the opening address.

Over the past several years, TWAS has focused special attention on the challenges faced by young scientists in developing countries, especially those countries with weak scientific capacity. We hope that these efforts will help nurture the next generation of scientists in the South. In partnership with BioVision, TWAS provides support to the best young scientists from developing countries to attend this annual event. Last year, we supported their attendance at the BioVision Conference in Lyon. This year, we are supporting their attendance here in Alexandria. I can think of no more important task if we are to successfully address the overriding theme of this conference: 'The New Life Sciences: Future Prospects.' I am particularly pleased to note that the conference will focus on such key issues as health, food and agriculture.' These are areas of critical concern to the future of the developing world.

The scientific community has become increasingly obliged to assume greater social responsibility, as science itself assumes a more central place in a world where progress is driven by knowledge. It is in this spirit that I look forward to the discussions that will take place over the next few days here in Alexandria. Let us raise questions and issues that match the challenges we face, and let us search for solutions and opportunities that benefit all humanity.

A New Strategy for Life Sciences R&D

Koji Omi

It is a great honor and privilege for me to be here at the opening ceremony of BioVisionAlexandria. From the time I served as Minister of State for Science and Technology Policy in 2001 and 2002, I have been deeply involved in the formation of science and technology policy in Japan. I had a long career in politics and now I am devoting myself to science and technology policy. I am also the founder and chairman of the Science and Technology in Society forum, also known as the STS forum.

As if well-known, Japan lacks natural resources and therefore human resources have been the key factor behind our present-day prosperity. It is expected that those human resources will be the source of innovation and lead to value creation in our society. Against this background, the Japanese government has always regarded science and technology policy as one of its key policy agendas, because promotion of science and technology will improve industrial competitiveness. I myself was instrumental in the enactment of the Fundamental Law for Science and Technology in 1995.

I have also been committed to promoting science and technology in Japan and since then achieved the goal of doubling the core science and technology budget.

Thanks to this and other efforts, a system is being created in Japan in which science and technology policy is promoted as a comprehensive national agenda, in a concerted movement involving various ministries and agencies.

In Japan, the Council for Science and Technology Policy, chaired by the Prime Minister and with major cabinet ministers and leading figures in academia and business as its members, is the central organ for setting science and technology policy.

The Council announces its Basic Policy every year, prioritizing the areas for targeted actions. The most recent basic policy was announced in January 2010. The main features of this basic policy are 'Green Innovation' and 'Life Innovation.'

'Green Innovation' refers to technologies for tackling environmental issues including climate change. This not only covers specific technologies like photo-voltaic cells and efficient batteries, in which Japanese companies have excelled, but also extends to systems development such as the smart grid for electric power. Green biotech has a place in this initiative. A new manufacturing process with reduced burdens on the environment and fuel production from bio-based sources are examples that come to mind immediately. In addition, the development of climate-resistant, high-yield plant varieties through bioengineering can contribute to relieving the worldwide food shortage. Furthermore, under this initiative, the development of high value-added plants that can produce pharmaceuticals and food with health-promoting benefits is envisaged.

'Life Innovation' refers to promoting technologies to improve the quality of life in the health, medical and welfare fields. In particular, the importance of the life sciences is highlighted in the area of drug discovery and regenerative medicine.

'Life Innovation' is part of Japan's basic policy for science and technology, but that is not sufficient. In order to translate this initiative into concrete measures, the Japanese government will establish an action plan in the next few months. This action plan is not just a roadmap for governmental support. Rather, it aims to developing a comprehensive plan for using the specific outcomes of research and development. While discussion of the action plan has just started, let me share with you some of my ideas about prioritization. In my view, there are three areas that call for immediate attention: bridging the gap between basic research outcomes and clinical needs; promoting personalized medicine; and overcoming institutional barriers to innovative drug development in Japan.

The first of our challenges is how to bridge the gap between basic research outcomes in the life sciences such as genome studies and actual clinical needs, including drug discovery.

At the turn of this century, there was a breakthrough in analyzing the human genome, leading to the complete sequencing of human genes. Many in the private sector rushed to capitalize on the practical results of this project. US-based venture companies such as Genentech and Amgen emerged. They have been enormously successful in applying the findings of genome science to actual medical practice.

However, this has not been the case in Japan. While there have been many important findings as a result of basic research in life sciences at universities and public laboratories, the private sector in Japan has failed to utilize them in medicine or drug discovery so far. However, to help apply new technologies to drug development or medical treatment, different ministries have started to collaborate. For example, ministries have meetings to discuss iPS cell research and development. In the project for a drug screening system using iPS cells, a user forum consisting of major pharmaceutical companies has been established to quickly apply the outcome of this drug screening system to innovative drug development.

Including but not limited to iPS cells, different ministries are also collaborating to promote translational research among universities, public laboratories, hospitals and enterprises, going beyond their traditional turf. However, their efforts need to be accelerated and aimed at further institutional development. A major challenge remaining in Japan is the need for developing venture enterprises that can shoulder the role of bridging the gap between innovation and application.

To address this situation, the Innovation Network Corporation of Japan was established in July 2009. This new public-private organization promotes 'open innovation'—a concept in which companies use both external and in-house ideas to advance their technology. The private-public funds for the Innovation Network Corporation will be used to promote advanced technology across companies of all sizes, as well as among universities and research institutes, with the goal of rapidly developing and commercializing the technology. The Japanese government has invested 800 million US dollars in this corporation, with an additional facility of US$8 billion in government-guaranteed loans.

Life sciences are one of the priority areas for investment by the Innovation Network Corporation. I am hopeful that bio-ventures in Japan will become more active with investment from the corporation, overcoming the so-called

'Valley of Death' problem and bridging the gap between basic research and clinical application.

Second, let me turn to the subject of personalized medicine. Rapid progress in genome science has led to discoveries that there are differences among individuals in terms of propensity to develop diseases and drug efficacy. Based on these findings, a brave new world of personalized medicine is developing in front of us. Coupled to this, progress in imaging technology, as well as information and computer technology, has enabled us to use elaborate analysis in clinical applications for personalized medicine—something that was completely unimaginable just a few years ago. Medical treatment in the future will definitely be personalized, and life sciences will play an important role in its development, including new drugs discovery.

The development of an appropriate biomarker could, for instance, lead to an early diagnosis of anomalies in a small quantity of proteins in the blood. This would in turn enable doctors to treat disease at a very early stage or to prevent disease from developing. This will dramatically change the shape of medical practice from diagnosis to treatment to prognosis, reflecting individual differences. While this is a blessing for many of us, it will certainly change the way we live and how our society is structured.

I must address the issue of institutional barriers that exist in Japan that are preventing us from acquiring the fruits of life sciences research.

In Japan, it is often the case that clinical trials and the approval process under the Pharmaceutical Affairs Act are too costly and time-consuming for new medicine, new medical devices or an innovative technology such as regenerative medicine to take hold in clinical applications. To overcome these barriers, we need a completely new approach for facilitating clinical trials, including focusing on more positive utilization of larger hospitals, enhancing the financial support system for hospitals performing trials, and promoting international clinical trials.

We will need regulatory reform as well. Personnel must be substantially increased for regulatory supervision. We will also need to revisit the current regulatory system with a view towards making adjustments easier and quicker to reflect the rapid advance of technology. We need to pursue the best mix of regulation and innovation through achieving sound regulatory science. We are proud of our secure safety culture in Japan and we need to build on this good tradition. However, we need to review the whole regulatory system continually so as to make it more rational for the purpose of promoting innovative medical technologies that are truly beneficial to patients.

Finally, I firmly believe that BioVisionAlexandria will help us develop deeper insights into the life sciences through broad-ranging discussions. This gathering will also be conducive to build up mutual trust among the participants here.

In closing, I sincerely hope that this conference will mark an important milestone for the global community to take advantage of the potential that the life sciences have to offer.

Interpreting Gene Sequences: Speeding up the Snail's Pace

Richard Roberts

Although the first bacterial genome was sequenced in 1995, we still lie at the very beginning of the era of genomics. It is now routine to obtain complete and accurate sequences for the genomes of small organisms such as bacteria, archaea and even the lower eukaryotes such as Saccharomyces cerevisiae. These complete DNA sequences are of great importance because they contain the genetic blueprint for the organism. Importantly, not only do they tell us what genes are present in the organism, they also tell us which are not.

However, to properly interpret this information, not only do we need to identify exactly which parts of the DNA sequence encode the genes, but we also need to know what the genes are responsible for. What proteins do they encode and what are the biochemical functions of those proteins? Only when we have this information, we will have the fundamental building blocks upon which to base our understanding of how the organism works.

Thanks to the technological advances that began with the development of DNA sequencing methods in the mid-1970's, DNA sequencing is getting faster and cheaper, but disturbingly the accumulating sequence is greatly exceeding our ability to interpret the final product. This is well illustrated by looking at any recent bacterial genome sequence and seeing that the number of predicted genes that have unknown, and in most cases unpredictable function, is often 20-40% of the total. This is about the same number that we found in the mid 1990's when the first bacterial genomes were sequenced. Thus, while sequencing techniques have vastly improved, the interpretation of those sequences continues to make progress at a snail's pace. We have spent a huge amount of money developing better sequencing methods and drastically reducing the costs of sequencing, but there has been no such investment in understanding the function of those sequences.

Increasingly, we have been content to rely on computers to look for similarity between old genes and new genes and simply assumed that if the two genes were similar, then they must have the same function. This has led to many known cases where an initial assignment was incorrect and now hundreds of assignments are similarly incorrect because the original problem was propagated. Even more disturbingly, for those genes with no known function and no easy way to predict a function, they have simply been ignored for the most part. There has been no systematic effort either to predict or to determine experimentally the function of those genes.

One might ask why this is the case? There are several reasons. First, de novo prediction or testing for function is not a simple matter. Predictions can be made in many ways such as locating small characteristic elements within a sequence that might suggest interaction with a possible substrate. Sometimes the neighborhood of the gene can be helpful as when a gene lies in a well-known operon in which the functions of neighboring genes are known. Occasionally the structure of a protein can give some clues to function. But in all these cases, the biochemical challenge remains that often a good deal of experimentation is required to test and hopefully validate the predicted function. More significantly in the current research climate, there are no really good high-throughput methods that allow the function of large numbers of genes to be tested experimentally. The result has been that we still rely on the serendipitous discovery of new functions for genes instead of adopting a dedicated and systematic approach to fill in the void.

In 2004, I suggested a solution to this dilemma in which high-throughput might be achieved by parallelization of low throughput traditional biochemical approaches. That is, a large number of individual biochemical labs might be corralled to test specific computational predictions that lie squarely in their area of expertise (Roberts, R.J. (2004) Identifying protein function—a call for community action. PLoS Biology. 2: 293–294). I proposed that a database of predicted functions could be assembled by computational biologists and that expert biochemists could then browse those predictions and find ones that were easily testable in their laboratories. They could then be awarded a small grant, perhaps $5-10,000, to support a student who, under the expert tutelage of the laboratory, could quickly test the prediction.

This idea was sufficiently appealing to *NIH* that I was encouraged to organize a workshop in Washington to explore it further. My colleague, Simon Kasif, a computational biologist from Boston University, and I organized such a workshop in 2004 and a report was issued by the American Academy of Microbiology. Many grant administrators came to this meeting, expressed interest in the idea, but told me that they were ill-equipped to administer small grants and so the idea was shelved. However, in 2008 a Request For Proposals (RFP) was issued by *NIH*, under their Grand Challenges Initiative, that asked for novel approaches to the functional annotation of genomes. At this point Simon Kasif and Martin Steffen, from Boston University, and myself decided to pursue my original idea and respond to the RFP. We were fortunate to get it funded and the result is COMBREX a project that aims to provide functional annotation of bacterial and archaeal genomes through a grand collaboration of biochemists and bioinformaticians.

Under the leadership of Simon Kasif, the computational challenge of building the database of predictions is already well underway. A number of expert bioinformaticians have already joined the project and more are expected in the future. At the same time, Martin Steffen and I are organizing the biochemical testing of these predictions. We already have a few collaborations underway and we anticipate that there will be many more in the future. We hope that the COMBREX website, which is currently being tested by our collaborators, will be completely open to the general public by the end of August and at that time we expect to receive 'bids' from biochemists that have the expertise to test predictions.

Under the current funding model, a biochemist wishing to test a prediction would receive a small grant to pay for the incremental cost of bringing a student, perhaps a rotation student, or even an undergraduate, into their lab to perform the necessary biochemistry. The proposal that the biochemist would submit would be fairly brief and would outline the experimental approach to be pursued to test the prediction. At that time, the gene or genes chosen would be off limits for six months and no other bids would be allowed until the first laboratory reported its results. Those results would be posted on the COMBREX website, irrespective of whether they are positive or negative, and we would also encourage publication of the results in the scientific literature. Indeed, we are contemplating initiating a journal specifically dedicated to such efforts.

It is important to note that because this initiative is currently being funded with U.S. funds, only U.S. laboratories have the opportunity of obtaining funding through this mechanism. However, the possibility of picking a gene to test will be open to everybody, including laboratories in Europe and the rest of the world. We hope that some young Egyptian scientists will join us! We are encouraging other funding agencies both within and outside of the U.S. to also make funds available to support this project and we have found good interest from both the Wellcome Trust in the U.K. and the Howard Hughes Medical Institute in the U.S. As time goes on, and if the model proves effective, we anticipate that a number of non-US government funding agencies might also be prepared to throw small amounts of money into the ring to support this effort.

At the present stage, the effort is limited to genes in bacteria and archaea mainly because these are more straightforward to identify. Functional predictions are often easier to make and certainly producing the proteins encoded by these genes in fully functional form and hence available for biochemical testing is generally quite easy. However, if the project is as successful as we imagine, then it could easily be extended to eukaryotic organisms.

It is obvious from the previous description that what we are doing under the auspices of this project is not just providing experimental determination of gene function, but we are also building a community of bioinformaticians and biochemists eager to collaborate on this important project, which will impact all aspects of biology. Importantly, as more functions are elucidated, so our ability to make better predictions will increase. There will be a synergy between the two fields that should benefit everybody.

I am reminded of my own early days in biology when collaboration was the norm. Because biology was still a very small field at the time, everyone' was quite keen to share results, reagents and ideas so that progress could be made quickly. It is our hope that this COMBREX project can revive some of this collaborative spirit which was so successful in driving the early developments in molecular biology.

That basic understanding will also enable us to manipulate those organisms in a sensible fashion. For example, a good understanding of the human genome will be the basis for personalized medicine. From plant genomes we can probably design new pathways that will lead to better foods and perhaps even energy production. From the myriad of organisms in the oceans we can expect to find many novel genes that may lead to new medicines and also may impact energy. Increasingly we are realizing that all the large organisms we typically think of live within a millions of bacteria and archea that affect, in a very significant fashion, all of life on Earth. Their genomes offer particular promise in areas such as health, food and energy and have the great advantage that being small one might hope to gain a good understanding of how these organisms work.

2

BIOVISION COMMENTARIES

1

The Third Global Revolution

Ismail Serageldin

We are living the third global revolution. The first revolution was agriculture, which allowed societies to become sedentarized and civilizations to rise. The second global revolution was the industrial revolution which transformed not only the means of production but the relationship between humans and the products that they work on.

The third global revolution is the knowledge revolution. We are witnessing an amazing transformation right now where the emphasis is no longer brawn as we would say or muscle but brain. This is where it's coming from and it is having a major impact in transforming industries, in creating new sectors in areas which didn't exist before.

The revolution that we are living is just beginning. The speed of change is phenomenal, the interaction between science, technology and innovation is great. Sometimes it raises fears in society about the ability to cope with that speed as practically everything we know gets transformed within a few short years.

We talk about the information society or the knowledge society. Data when it gets organized becomes information, when it's explained it becomes knowledge. But is that enough? What we really need is wisdom. Wisdom is beyond knowledge. It is in addition to knowledge. The world we live in however is one that contains a lot of knowledge but perhaps not enough wisdom.

It is a globalized world where boundaries have been transgressed in many ways. We know the problems; financial markets that have gone out of control, a feeling among many in the developing world and even in the industrial world that the poor are left behind and unable to cope whether they are in the rich countries or in the poor.

In the meantime lifestyles continue unabated, both in energy consumption, in means of transportation, in destruction of our patrimony of natural resources and in our continuing pollution and its impact on climate change and the greenhouse gases and also pollution of the most vital thing for life and that is water.

Sadly we are still spending enormously on the military. 16 times more on military spending than on development assistance around the world today with horrible impacts. Yet despite what we know about the cost of war, it continues. People can always find money for it. This to me is one of the most moving pictures I have seen but then of course I am a librarian so I am deeply moved by the child holding the books.

I think that it is depriving also human rights, it is not just political and civil rights but access to knowledge, ability to learn and to flourish is part of human rights. I world say that it is not enough to celebrate the Earth and its inhabitants, that we must restore what we have destroyed.

We can see the possibilities, we have an unlimited transformation in our ability to communicate around the world. There is a gaining ground for the notion that we have a common humanity and all should share in human rights, a global consensus was formed not just about the Universal Declaration of Human Rights in 1948 and subsequent instruments but even about the Millennium Development Goals and yet my friends, the first and most essential of the Millennium Development Goals; the one that would try to fight poverty and hunger is going the wrong way. Now why is this because in fact what we need above all to implement these images, these goals, is peace. I call a witness that you will all recognize and not just because it is the year of France and Egypt, Napoleon Bonaparte is probably one of the best known figures in history and a person who actually used the sword somewhat. What you may not know is what he said reflecting on his life. He said: 'Do you know what astonished me most in the world? The inability of force to create anything. In the long run the sword is always beaten by the spirit.' So on reflecting on his life, Napoleon found in fact that the lasting contributions he made were those of the foundation of Academies of science, foundation of National Theatre, the Central Bank, the Code Civil

There is no security without peace, there is no peace without justice, there is no justice without equity and there is no equity without inclusion. People must be included in the processes that affect them or else there will be no lasting peace. With that the future really can be great. Technology is very promising. We already connect young people everywhere in tools that nobody could imagine would exist. We expanded our brains' reach in avenues, and means that are beyond belief and a whole lot more. The current moment I know people will say we have had terrible impacts of the financial crisis. But I see a silver lining in it, global markets on the knowledge-based economy that got people to see the trillion dollar markets and maybe yes they did go overboard in unchecked fashions and they did blow a fuse in the financial markets of the world and at huge cost to people, in real costs in terms of unemployment and other problems.

But there is a silver lining. For the first time we are really able to have a proper debate on the role of government, regulation and the private sector.

Secondly, we have a new administration in the United States which is willing to look for multi-lateral solutions recognizing that many of our problems cannot be resolved by a single country no matter how big or how powerful it is.

Thirdly, there is a greater awareness that global environmental problems will require collaboration across boundaries and that in fact we must all get together even if that has escaped us in Copenhagen. So the best outcome would be new opportunities for the South, for the Developing World but only if the South can master Science, Education and develop its own scientists. Here we are facing inequality of access to resources. If rich countries in per capita income have 40 times the income of the poorer countries, they are actually spending on per capita terms 220 times more on research every year. That is an amazing figure and yes therefore there are some of the poorest people in the world; that lowest billion that is still hungry today is being left behind and the mystery of economic growth is that it is lifting up many parts of the world, including huge of humanity like China and parts of India but it is leaving behind others. Inequality of access to equipment. Here is a preschool in Germany and here is a school in Sub-Saharan Africa without even a black board, without places to sit on, no chairs for the children. And vast numbers of young children who are in fact competing to find their place in the sun and to learn and maybe technology will provide them with answers. There is inequality in access to knowledge. Teachers in many parts of the world need recent correct and easily available material. We are doing our part and there will be a discussion of the Supercourse later on.

So the future is there, the challenges are here. What do we do? For one thing we are having this meeting and getting together to share ideas about how we can actually make this happen. This is the fifth BioVision we organize in Alexandria. They have all been well-attended I am happy to say. We also have our Biofair and poster sessions for younger scientists. The publications from the previous events show the quality of the work that has been done in these previous conferences and I have every reason to hope that this one will join the rest

But fundamentally what we want to do is to address the new knowledge revolution. For the biological sciences are poised for a transformation that has no parallel in history. Whether it is the knowledge or the method or the history, they are intertwined. It is very difficult to take them apart. Here in this conference we will have themes that will come back and forth and are woven together. Themes of medicine, health & education; agriculture, food & natural resources of technology, industry and environment. Where as in BioVision Lyon we try to have practicing scientists, researchers, as well as CEOs of industry being present as well as members of society at large like myself. I can cover several of these but nevertheless. The themes are intertwined and you will find therefore reflections, it's not just completely cut out, you will find reflections of these issues coming back and forth in the various sessions. Key questions: How does new knowledge generate new technology and how do new technologies impact these themes and how do these three groups of actors relate to each of these themes. and if we can immediately see tomorrow can we dream of beyond tomorrow? I think we can and I am very happy to welcome in our midst a lot of very distinguished people who are working on Biorobotics who will show you a glimpse of something we thought was in tomorrow but is beginning to happen today.

Let me start with the theme medicine, health and education. I will ask those who address it to keep in mind the following questions.

The first is the global challenges and the priorities in research. Well we all know that medicine is advancing, it has life-saving potential, we all know that we have benefitted from various kinds of medicines, perhaps that is the most widely used medicine in the world; aspirin. It is important to understand the cost, the obstacles of getting new medicines developed but will they be within reach of billions of human beings who need them?

Second as was just mentioned by our minister: the brain drain. We want to turn the brain drain into brain gain whether by circulation or by collaboration. This is an interesting graph that shows co-authored paper with the US and the percentage of foreign-born PhDs in the US from that country. You may think it has a direct relationship but actually what interest me more is looking at that. Why for the same percentage one group of countries is getting 4-5 times more collaboration than another. What can we do to ensure that this collaboration actually takes place and that therefore brain drain is transferred into brain gain and then hopefully later on into brain circulation.

New Knowledge, new technologies it opens amazing new possibilities but is it affordable? Because that brings us to the access to medicines questions which is an important issue. It was mentioned by Christian Grenier at any price, what price what does it cost and there are ethical about clinical trials being done in developing countries by rich countries. We need to think about that and think about priorities.

I am very happy I dug up that picture Elias Zerhouni and myself had the privilege of being with Bill Gates in Davos in 2003 in the launch of the Gates Foundation Global Health Challenges which resulted in setting priorities and now the Gates Foundation has become the biggest donor in assisting health in developing countries (Figure 1). Mobilizing the genetic revolution is the challenge that we have to think of, not just the conventional chemical remedies of the past but can we in fact find ways of dealing with that?

Figure 1

That brings us to a way that we have been working on some of us: Education, Epidemics and Action. Why epidemics, you will know very soon. My friend Ron LaPorte is here, he is the founder of what we call the Supercourse. The Supercourse is basically a series of PowerPoint lectures that are made available for free on the internet, available to anybody around the world and is governed by a community of practice and we create these DVDs and send them to people for free. We send them to deans in medical schools around the world. The WHO has helped send them all over the world but these are to get them in DVD form but they are online in 34 servers, 3600 lectures, used by 60,000 teachers to reach a million students in 175 countries for free. What are we planning to do? There was epidemiology, we want to expand it not just to deliver the written material and Ron LaPorte and Gilbert Omenn and Vin Cerf who is not here with us but Gil and Ron are here and myself, are committed to try to expand it to other areas including medicine, engineering, IT, environment and agriculture to build communities of practice which we hope will include you and get them to contribute in what we are doing.

A large part of that contribution is work that has already been done. All of the distinguished scientists here are using PPT lectures anyway so what we want is to get copies of your lectures to be allowed to be given for free to be utilized by people and we will be launching some spectacular new functionalities to help you use it and contribute to it. Come and listen to this session on the Supercourse.

Theme II on food, agriculture and natural resources is really addressing the need for us to challenge what is happening in global agriculture. I was very happy to be with Dr. Adel El-Beltagy and others in Montpelier two weeks ago. We have an unfair, unsustainable system of agriculture in the world. That's to make it simple and straight. How? We know the numbers, we know the challenges. The question is how do we transform agricultural research into development to respond to these challenges? That was the theme of Montpelier.

The first of these is to recognize what went wrong with the food price crisis of two years ago. It was a devastating experience. Well it exposed the weakness and fragility of the current world system. First of all it distorted trade that we know of, that we worry about in terms of subsidies. This cartoon done by Zapiro of South Africa is very indicative of how third world farmers (Figure 2) are expected to compete with highly subsided, highly mechanized first-world farmers. But shortfalls in production, draught in Australia and elsewhere, low global food stocks against a rising demand for food and feed with prices spiked. Now countries slapped on export bans and that immediately exasperated the situation and has now fed a paranoia in importing countries that should that be repeated there would be no guarantee that even if we are willing to put up the money we will be able to find the food we need. And thus contrary to trying to optimize global production people are moving back towards notions of self-sufficiency rather than being able to think differently about food security.

Figure 2

There is a huge increase in demand for animal proteins due to high increases in incomes in many parts of the world especially in China and that would result in needs for feed because most animal proteins today are produced by animal feeds through farming. That puts a special weight on maize or corn and we add to that that there was a very unfortunate switching to biofuels with an emphasis on switching to corn which also helps the spike on food prices that occurred and that led to the Tortilla Riots in Mexico in 2007 and here in Egypt we had our own echoes of that at the time policy to this day.

My friends, it is wrong to burn the food of the poor to drive the cars of the rich. It is simply wrong. We need a second generation of biofuels. I think there is a lot to be done from cellulosic grasses to biodiesel to algae. There is a lot of very interesting prospects that need to be done. We need to advance on biofuels not in this way. There is biomass. There is a lot of other forms of biofuels but we need to think of it without polarizing the issue around these issues.

So we need fair trade, sustainable production, improved access for all and hopefully out of that we will be able to go back to that first Millennium Development Objective which was to abolish hunger. Regretfully the Millennium Development Goal was cast in 2000 to reduce the number of hungry people from 850 million to 425 million instead of which it has gone up to 950 million and now has crossed the billion mark in terms of people who are chronically malnourished.

An enormous gap exists between rich and poor in the countries. Not globally because the movements in China and East Asia have affected the global figures but within China, within India, within Africa, within Egypt. 96% of the countries as reported by UNDP have had an increase in the gap in the income distribution internally, between the rich and the poor countries.

Only very few have been able actually cope with that. So despite global production and despite the fact that technically food would be available. In fact plentiful or not, it is not available and even now in certain parts of the world. We are facing now a specter of the return to starvation with images of that kind (Figure 3).

Figure 3

So what can we do in terms of policy that links science, agriculture and research in order to tackle that issue better? We need to link research into development, that was what was said in Montpelier. We need to focus on small-holder farmers, they are disproportionally poor but also produce most of the food that is consumed locally and urban poverty is impacted upon by the capacity of increasing the productivity of the poor farmers.

So we need to raise agricultural productivity faster than way the reduction in prices. So that the poor farmers can benefit and the poor who buy the food would increase their access. And we need to measure that in terms of total factor productivity. Land, Water, Labor, Energy and Chemical Inputs should all be factored in.

If we improve the nutritional content of the food, there could be inormous the health benefits, biofortification is just beginning as a new technique that we are just studying nowadays. Of course the most famous of these case was Vitamin A rice and there are others. And we need to also address beyond that the vulnerability of many farmers in the developing world.

In Egypt we rely almost entirely on irrigation but in many parts of the world people are dependent on rain and rain fall and that is a problem. In environments such as in Sub-Saharan Africa they are totally dependent on rain fall and rain fall has been erratic and variable but more importantly over time there is a reduction in global rain fall which poses serious problems. So we need to find ways by which extension must bring research to the farmers, small holder farmer and all should benefit from that result including the poor in the cities by lowering the price. And that means we have to transform our extension services. How do you link the research to the actual farmers so the farmers benefit and adopt it.

M.S. Swaminathan who could not be with us today but is a friend to so many of us as we are going to celebrate his great partner, the passing of Norman Borlaug in a special session. He said we are all on this Earth as guests of the green plants and those who tend them. If you reflect briefly just how true that is, you wonder why those who tend the green plants are so low in the totem pole in our developing countries. Yet they are the ones who are making us all live.

So agriculture is the key to poverty reduction, to environmental stewardship and food security and women are the key to food security and agriculture because they play a central role in Sub-Saharan Africa. They produce 80% of the food, they receive 10 % of the wages, they own 10% of the land.

Small Scale production can be replicated on a massive scale. We saw that in the case of Grenienne and the dairy in India which now out produces in the United States, mostly by organizing small holder farmers.

Research for the poorest is particularly important and we haven't focused on that yet because the poorest do not respond easily to market incentives.

There is beautiful economic work by Partha Dasgupta done on that. That's why trickle down doesn't work for them and special outreach programs are needed to reach people who are in this level of dire poverty around the world and are at risk of in fact going hungry and potentially of starvation especially now, politically again I get back to my statement about peace. We have now more people who are displaced, which the UN euphemistically refers to as IDPs which kindly takes the edge off of it but I like to see the picture, I like to see the real human beings behind it. We have are tens of millions of people who are displaced in their own countries because of civil strife, if not outright war.

As I mentioned a moment ago gender is extremely important to tackle these kinds of issues. It is in the end practically in every of society the women who build the social capital, who weave together that network of relations that make the society function and empowering women is essential to result in major improvements in school enrollment, infant mortality, child morbidity, etc..

Women today in most developing countries have unequal access to education, health care, income, credit, employment, assets, decision-making. Almost every field that you can think of. They suffer from the absence of proper systems of water, they suffer because they have to take to market in non-existing conditions, they suffer because they are the ones who are responsible not only for feeding the children but also for their education and their future and it is their solidarity together that keeps of these parts of the world going and allows the transfer of good values of collaboration where others would see conflict.

Biotechnology is of course one of the most obvious applications of the new biology. It has a lot of promise and its increasingly being applied in very large areas and if we are thinking of the future challenge to produce more food with less water, less labor, less chemicals. With an increasing population. How do we deal with this? We can raise the yield ceiling or you can try to close the yield gap between the current average and the potential that is established in extension stations and you have to invest in sustaining the current yield because if you do not constantly invest in research the current yield will drop.

So we need technologies for increasing the yield potential, sometimes it comes from different plant types, so called super rice structures, fewer tillers, more grain. New plant types can increase significantly the output. This is what we have 15.2 tons/hectare. Egypt today leads the world in terms of rice output. We have to understand where the losses come from. Whether its weeds, disease, or insects. We can find ways of fighting Bacterial Blight with transgenics. Here is an example of how Bacterial Blight Resistances can be tagged with molecular markers. How we can find resistance genes very effective against that. We can see Stem–Borer damage and here we see the Stem–Borer Larvae from the Transgenic Rice and the Stem–Borer Larvae form the control rice below so we can fight pests in non-pesticides using ways.

But also integrated pest management. We want to maximize the use of eco-friendly strategies and minimize the use of toxic chemicals. Biological controls therefore are important, this is a conference on biology we need to study more of that. But always remember we should talk in terms of total factor productivity, land, water, labor, energy and the chemicals that go into it. We need technologies for all of that if we are going to significantly increase the productivity from the same amount of land and water that we now have and without being as disruptive and unsustainable as we are.

If we improve the nutritional content it will have great health benefits and it may even go beyond just food and into vaccines. I mentioned vitamin A rice which could not have been done without transgenics. That was the work of Ingo Potrykus and Beyer, and I also want to mention that this is not the only case. It's also available in sweet potatoes with and without B-Carotene. There is also high iron rice. The two pigs are twins, one was fed regular maize, one was fed quality protein maize (Figure 4). I think that is quite compelling as an image of what better nutritional content can do. That these twins have grown this way.

Figure 4

We have barely tapped the potential for fish-farming and sea-farming and we are still artisanal in many of these things. But there is a lot of promise for longer, more productive lives. But that has to be done working with natural resources. We are already major disruptors of the eco-systems of the Earth and probably what's important in environmental action is to reduce the need for bringing more land under cultivation as it will not be a way of producing more grain but there may be losses in biodiversity, in soil erosion and water is so important. I'm very glad that many of the world's water-leading experts including Peter Gleik are here today.

Agriculture uses about 65–70% of the water today. In developing countries it was 80–90% of the water. For our food about a liter/calorie is what we need. So an average person consumes about 2700 calories. To produce them we need 2700 liters a day and we know already the problems that exist in areas like China, the yellow river and as early as 1997 did not reach the sea for 220 days.

In Egypt the Nile has to reach the sea because it washes out the salts of the delta and it reaches Cairo with 12 million tons of salt and reaches the sea with 34 million tons of salt. If it did not carry that out all our prime agricultural land would salinize.

We are still using a lot of water. This is an average image of a rice field (Figure 5). We are pumping underground water in many parts of the world to do this. In Syria water tables are dropping a meter a year for the last 30 years and this is what it looks like.

Figure 5

Figure 6

This is an image I like (Figure 6) a lot because people don't understand what is lowering water table. This is a communal well in the Sahel and the people have dug deeper and deeper and get a few drops of muddy water from the bottom. And when that will disappear then of course you will have desertification and environmental refugees. Currently it is between 2000 to 4000 tons of water to produce one ton of rice, 1200 tons of water to produce a ton of wheat on average. We can do much better than that. The simplest, most immediate way is to shorten the growth duration, to find levees for water management in uneven field to do land leveling and soil-puddling for transplanted rice, the sowing of rice.

But reducing pollution is also essential. This is an important part of the CGIAR work because people assume that the CGIAR tells people to use more pesticides which it does not. In fact it argues that dropping pesticide use does not drop the yield of rice beyond a certain level. But all of that is being swamped on the environmental side by what is happening to climate change. Climate change is the most serious issue facing humanity. Despite the fact that some figures in the IPCC may or may not had been precise about whether it is in 2035 or 2070. The trend towards losing glaciers is real and the trend towards increasing storms is real. This is from the well-known scientific journal *National Geographic* which is a popular journal but it maps the hurricane tracks for 10 years 1985–1995 (Figures 7 and 8). And then the hurricane tracks in the same area for 1995–2004. First ten years, the next ten years and I think we can clearly see that is increasing and as sea-level rise

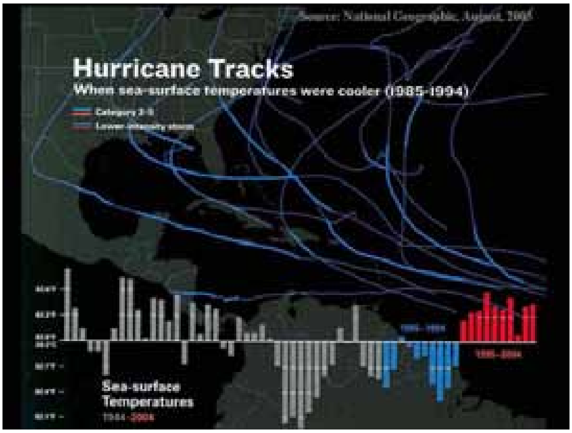


Figure 7

Figure 8

occurs what is going to happen to a number of countries including our own. Here is Alexandria for example, we will become a nifty little island because the sea will probably go behind Alexandria. Alexandria is still 2 meters higher but on the whole Delta you will have a major impact which if you can see here depending on the estimated rise and the actions taken that anywhere between several thousand km^2 of crop land could be lost and some millions of people affected. So what do could we do about that? A special session exists in that today.

The third theme is technology, industry and environment. Technology has been associated with production, with the industry. It was largely chemical in the past. This image was an advertisement actually for a plant in Bhopal (Figure 9). But it is the same plant that actually produced an accident on toxic fuels, one of the worst industrial accidents in history where 2000 people were killed.

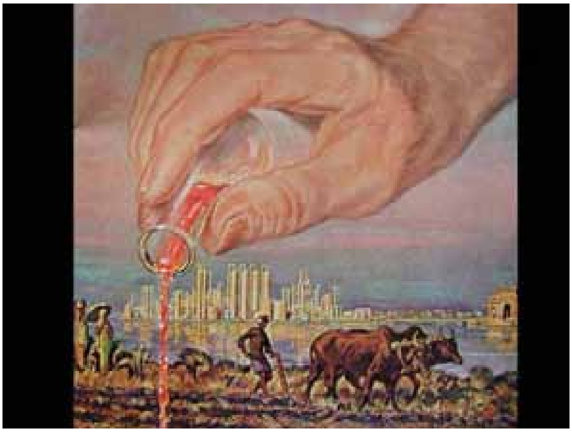


Figure 9

We know that there is the major problem of toxic waste management and when you burry it and it leaks you have these kinds of moon scapes where nothing can grow especially in Eastern Europe, in the former Soviet Union, some areas where radioactive material has leaked. So what can biotechnology do for us?

I don't know. But I do know that we are facing an era of convergent technologies which in Arabic is a nifty acronym because BINT means girly and we want to empower girls and women. But actually I meant Bio/Info/Nano Technology are converting in many ways and transformative research capable of changing the paradigm is taking place. So what is happening in these new industries?

Some of you may know the work of Dr. Mustafa El-Sayed using nanomolecules to kill cancer cells. There are other ways of dealing with that including everything from DNA computing to locking receptors on a cell. It is beginning to terminate a number of industries. Nano is growing fast. But do we know or have we reflected on what the potential impacts of nano might be on our bodies. If nano particles can go through cell walls.

New technologies, especially for water. What can we do? We have water needs, membrane technologies that will be discussed and several sessions that are devoted to that and many others a swell.

But science is advancing everyday on many fronts. Arthur Clark had this great quotation saying that 'Any technology that is sufficiently advanced seems like magic'.

Just reflect, if I told somebody 20 years ago that you could stand here, hold a little device that is a smaller than my hand and that you could—unconnected to any wires—just punch in a number and find one particular individual, out of the 6 and a half billion people on the planet and that the person would speak to you immediately and that you would be able to find that person whether they were in Australia or Europe or Latin America or in Cairo or next door. Most people would have thought that this is unbelievable. Today not only do we take mobile phones for granted we say 'Oh my God it's taking so long to get connection.' We have become very impatient.'

So there are many examples but in this conference we are going to have the privilege of discussing one particular area which is quite unusual which is biorobotics. Yes there is a search for artificial intelligence going on but there is also some very interesting work being done on Biorobotics.

Robotic equipment not only exists in factories as we well know but also in biological institutes, in the storage of samples and it's becoming cheaper and cheaper. This is a graph (Figure 10) from the *Economist* in 2008 that shows the cost of replacing human workers. In fact by robots. So the robots are here to stay and the question is how does the biology link to them.

Figure 10. Source: Economist 07 08

Rubinsky, Huan and Berkeley did the biotransistor back in 2000 and since then we have had the question of can cyborgs really exist. And we will hear from the real pioneers. Those who actually build robots for a living like Bruno Maisonnier and that's his little friend Nao whom you will be seeing tomorrow (Figure 11). Paolo Dario who mimics the studies of animals for the benefit of humans and Hiroshi Ishiguru who is designing geminoids which look exactly like humans. I guess the first application is to have one to sit on your desk while you go outside and let the boss think that you are still working but the geminoids are really good. You can't tell who is who.

Figure 11

But we have actually with us another great pioneer of a different sort, Kevin Warwick who can vitally be called I think the first cyborg because he has actually implanted a chip that interacts with his own body. Miguel Nicholelis is an old friend and pioneer who has been dealing with reading the brainwaves of monkeys and that to actual robots. Linking between the USA and Japan and many other fascinating experiments. He started with a beautiful small monkey called Belle on these issues.

But anything that deals with biology whether it is biorobotics or other things raises with ethical issue. I used to use this graph back in the 1990s (Figure 12) and I used to say where are we going in biotechnology? We are now in the second rung of this ladder. And I said, I think we will be assembling genomes like Lego pieces in the future and we used to laugh that we will be producing corn that looks like that (Figure 13). This cucumber is real (Figure 14). A lot of interesting things going on around the world. But assembling genomes has already happened and in June 2007 Craig Venter from the Venter institute talked about synthetic life forms and in fact filed a patent both in the United States and in WIPO on this.

Figure 12

Figure 13

Figure 14

The DNA molecule was constructed from scratch inserted into an oocyte and started to express itself. The purpose of that was to create new biofuels from single cell organisms and in essence the question is why not? Because we are already harnessing yeast as a factory and the doctors know that Artemisinin which is essential for Malaria is now done in yeast. Another and separate effort, George Church of Harvard is planning to do something and he started talking about the publication as of last year and we expect something this year on creating a cell from scratch. I don't know how far he is. Last time I spoke to him over a year ago he said that he was on track.

That's the synthetic part but the real life part, we and again here as a Librarian I speak, 'I am very happy to offer you the Encyclopedia of Life.' This is a major project with most of the big institutions in the world and the idea is to go on site, we have a homepage from which we can go to 1.9 Million pages each of which is devoted to one species. Behind that are 300–600 Million pages of scientific literature on biodiversity. That's the plan. That is how it will look like (Figure 15). At present we have about a 170000 of the 1.8 million pages have been digitized and about 30 Million of these 300–600 Million pages have been digitized in what we call the biodiversity heritage library and you can visit it in www.eol.org. Now we are working with the Arab Group to organize an Arab EOL as a contribution to it.

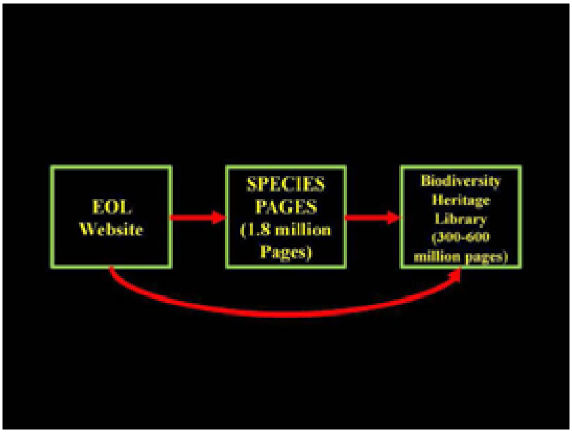
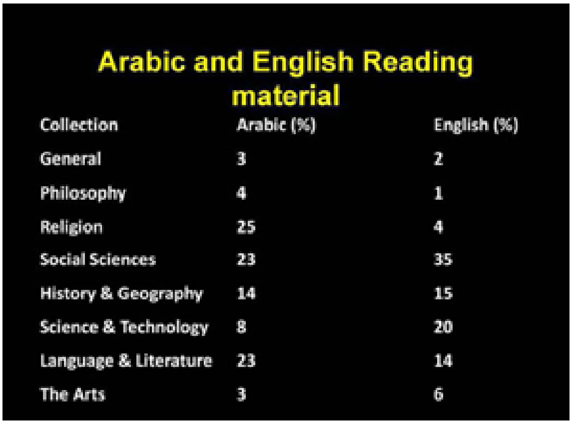


Figure 15

The first regional EOL was China, the second was with us for the Arab World and I am very happy to welcome the group of scientists from the Arab World working on Biodiversity who will be implementing this project into reality This is the Government structure that we have done, a committee with all major institutions, an executive committee that runs the day to day affairs then IT, libraries, translations, and science. With the science advisories advises the groups and then a connection with the biodiversity convention focal points and then the scientists are organized in working groups dealing with their specialties. We even have a Special TV Science Series Episode devoted to the EOL.

So my friends, science is advancing every day. The technology is like magic. The Arab World is falling behind. It's a fact, we have to recognize that. Let me show you why. This is the percentage distribution (Figures 16, 17 and 18) of titles of Arabic and English reading material and you will note


Arabic and English Reading material

Collection	Arabic (%)	English (%)
General	3	2
Philosophy	4	1
Religion	25	4
Social Sciences	23	35
History & Geography	14	15
Science & Technology	8	20
Language & Literature	23	14
The Arts	3	6

Figure 16

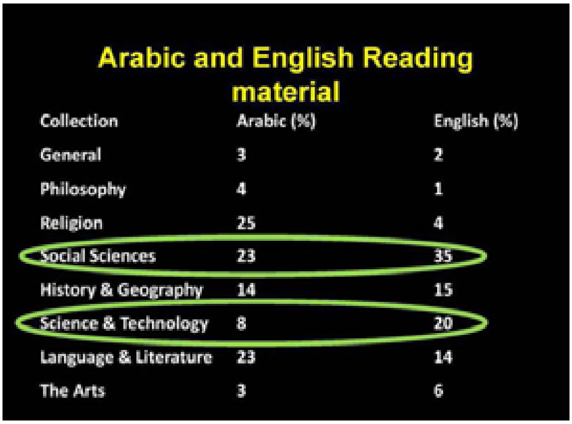

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Figure 17

Arabic and English Reading material

Collection	Arabic (%)	English (%)
General	3	2
Philosophy	4	1
Religion	25	4
Social Sciences	23	35
History & Geography	14	15
Science & Technology	8	20
Language & Literature	23	14
The Arts	3	6

Figure 18

that in science and technology we have 8%, they have 20. In social sciences the Arabic is 23 and they are 35. So 55% is in the sciences, whether social sciences or natural sciences. On the other hand in religion we have 25% and they got 4% and language and literature we have 23% and they have 14%. So you can see the relevant weight of that. So for all our Egyptian and Arab friends these are titles when you go to the book fair or when you go to the bookstores we will find 10 editions of 'Fatawy Ibn Taymeya'. Here they are counted as one. You will find 10 editions of 'Riad El Saleheen', it's counted as one. So that count even understates the imbalance in between science and heritage one could call it. So we are falling behind and that requires public education, the media unfortunately does not help educate the public sufficiently about these issues and scientists are not sufficiently engaged. The scientists are not reaching out and that's why we did our own TV series.

We need capacity support. Building capacity for science has to recognize these differences which I mentioned before. In some countries you cannot build capacity by collaboration and in some more proficient and advanced countries like Egypt you can build through collaboration. This has been studied by the Inter Academy Council. I have had the privilege along with the current president of TWAS and myself to present on behalf of all the scientists of the world, to Kofe Annan, the UNDP and the World Bank the findings of science on this and what we need are those five clusters. Science, Policy, Human Resources, Institutions, Recognizing the role of the Private sector and financing mechanism. They are all important. They reinforce each other.

On finance: what we need now part of the world is to recognize young people. In the US they have venture capitalists. Not only do they put pennies and receive huge amounts but they can recognize talent when they see it. So they look at this group of young people and that is Microsoft corporation 1978 and the question is would you have invested. Here is Bill Gates and he is just a kid like many of the we have here.

The question is if a bunch of young Egyptian or Arab youth came and said we have great ideas about something called Windows that is going to change the world and we need 2 million dollars. Would our industrialists give them the 2 million dollars do you think? Nowadays of course everybody wants to invest in Microsoft but in those days that's the thing.

So we need to be producers of knowledge not just consumers of technology. We need to transform rhetoric into action. We have had many past declarations, many governmental announcements but as my friend Zapiro had said it doesn't equal action. In fact it is a sad thing. I used this quotation in my statement with Jacques Diouf in Montpellier 'We have the capacity to eliminate hunger from the face of the earth in our lifetime. We need only the will.' President John Kennedy World Food Congress 1963. Today the number of hungry people has grown. Despite a global commitment by all the leaders of the world in 2000 to put it as the number one Millenium Development Goal. What went wrong? Luckily we have with us some real translators like Dr. Hani Helal and Dr. Hend Hanafy.

We can make it happen. Can we catch up in science? can we compete? I say yes. Korea did it. Taiwan did it, Singapore did it and we can do it. We here are proud to join with the artisans of a better future. So let us dare to dream, dare to be bold and we can do things differently and we can succeed. Now I remind you with two dreams that seemed impossible. Antarctica when it was so-called rediscovered. Immediately people wanted to bring in the bulldozers and the industry and the mining and minerals and money and build military bases and then a group of idealists including my late friend Jack Cousteau said no, let's keep the wilderness pristine, let's keep it for all of humanity, let's keep it for science. And people said are you out of your mind do you mean you want a whole continent just left to the penguins and he said yes and guess what we succeeded, we got the Antarctica agreement and Antarctica was not colonized as some people would have.

In 1963 those of us of a certain age who studied in the United States remember the battles for civil rights. The late Martin Luther King stood in Washington DC and said I have a dream and it was a dream. I have a dream that my children will one day live in a nation where they will not be judged by the color of their skin but by the content of their character. Well it seemed a faraway dream but it was actually realized. It happened and the audacity of hope must stay with us and Margaret Mead has told us never doubt that a small group of small committed citizens can change the world. Indeed it is the only thing that ever has.'

So let us out of this gathering move beyond the knowledge and the understanding to action. Let us work together for there is so much we can do for a whole generation and for the whole world and for the Egyptians and the Arabs here I say our youth may look weak and unprepared and the competition may look fierce but I say we shall surprise the world.

2

Merging Man and Machine

Kevin Warwick

In this article four different practical experiments in robotics and human/machine merger are described and then considered with regard to their ethical implications. Results from the experiments are discussed in terms of their meaning and application possibilities. The article is written from the perspective of scientific experimentation opening up realistic possibilities to be faced in the future rather than giving conclusive comments on the technologies employed. Human implantation and the merger of biology and technology are important elements.

Introduction

Science fiction has looked to a future in which robots are intelligent and where cyborgs – a human/machine merger – are commonplace – The Terminator, The Matrix and I, Robot are all examples. Until recently any serious consideration of what this future might actually mean was not necessary because it was not scientific reality. Now however science has not only done a catching up exercise but, in bringing about some of the ideas thrown up by science fiction, has introduced practicalities that the original story lines have not extended to.

Four different investigations in robotics and human/machine merger are described here. From a background of artificial intelligence, robotics and biomedicine, the author has been, in turn, an integral part of each of these experiments. In each case the need for discussion and debate on the issues raised is recognized. Hence the material here has been presented with a view to contributing to the area in order to provide a concrete basis for what has already been actually achieved to this point and hence what might be possible in the future.

Each experiment is described in its own self contained section. Following a description of each investigation the author has attempted to raise some pertinent issues on that topic. As can be seen, points have been raised with a view to near term future technical advances and what these might mean in a practical scenario.

Experiment 1: Future Identity

First is the use of implant technology, e.g. a Radio Frequency Identification Device (RFID), as an identity. This device transmits radio pulses which represent a unique number. The number can be programmed rather like a PIN number on a credit card. With an implant of this type the identity of the carrier can be specified.

Such implants are used, as a fashion item, to gain access to night clubs in Barcelona and Rotterdam, as a high security device by the Mexican Government or as a medical information source (approved in 2004 by the U.S. Food and Drug Administration) (Graafstra, 2007; Foster and Jaeger, 2007) – information on an individual's medication, for conditions such as diabetes, is stored in the implant. Because it is implanted the record cannot be lost or stolen.

An RFID implant does not have its own battery, but has an antenna and microchip enclosed in silicon. The antenna picks up power remotely when passing a larger coil of wire which carries an electric current. This power is employed to transmit by radio the signal encoded in the microchip. Because there is no battery, or any moving parts, the implant requires no maintenance – once implanted it can be left there.

The first RFID chip to be implanted in a human occurred on 24th August 1998 in Reading, England, in the author's left arm. The implant allowed the author to control lights, open doors and get a welcome 'Hello' when entering the front door at Reading University (Warwick, 2000; Warwick and Gasson, 2008). Such an implant could be used in humans for a variety of identity purposes – a credit card, a car key or (already the case with animals) a passport.

Experiment 1: Issues

The use of implant technology for monitoring people opens up a range of issues. Tracking individual people in this way, possibly by means of an RFID or, alternatively for more widespread application, via a Global Positioning System, by a Wide Area Network or even via the cell phone network, is now a realistic concept. Ethical questions exist when it is children, the aged (e.g. with dementia) or prisoners involved.

In the case of a missing child, who has been abducted, an implant could be activated to enable them to be located, saving their life – certainly saving a lot of police time and parental anguish. But is it appropriate for children to be given implants in this way? Shouldn't they be given the choice? In many countries children are, at a very early age, injected with chemicals (vaccinations) that we still do not fully understand and that have several side effects – this is ethically acceptable – why not a tracking implant to keep them safe?

The technology for implants to be used as an identity device has been with us for some time. As yet no credit card company has offered a major incentive, in terms of extra security or lower costs, for an implant to be employed in this way. It can be suspected that if a company did so do, there would be take up.

Implants for tracking people are still at the research stage. As they become available though there are numerous cases where there is a distinct drive, due to the potential gain, for a person to be tracked and their position monitored, especially where it could be deemed to either save or enhance their life.

Experiment 2: Robots with Biological Brains

When one thinks of a robot it may be a little wheeled device (Bekey, 2005) or a head that looks human-like (Brooks, 2002), which is operated remotely by a human or is controlled by a programme. In the first case there are few worries and in the latter case we feel that the robot will only do what it has been told! But what if the robot has a brain of neurons, possibly human neurons?

Culturing a brain commences by dissociating neurons from foetal rodent cortical tissue. They are then grown in a chamber where they have suitable environmental conditions and nutrients. An array of electrodes embedded in the base of the chamber acts as an interface. The neurons connect within a few days, giving useful responses for several months.

The culture is grown on an '8x8' Array which can be used for real-time recordings (Figure 1). It is also possible to stimulate the culture to induce neural activity. The multi-electrode array (MEA) forms a bi-directional electrical interface with the neurons (Chiappalone et. al., 2007; De Marse et. al., 2001).

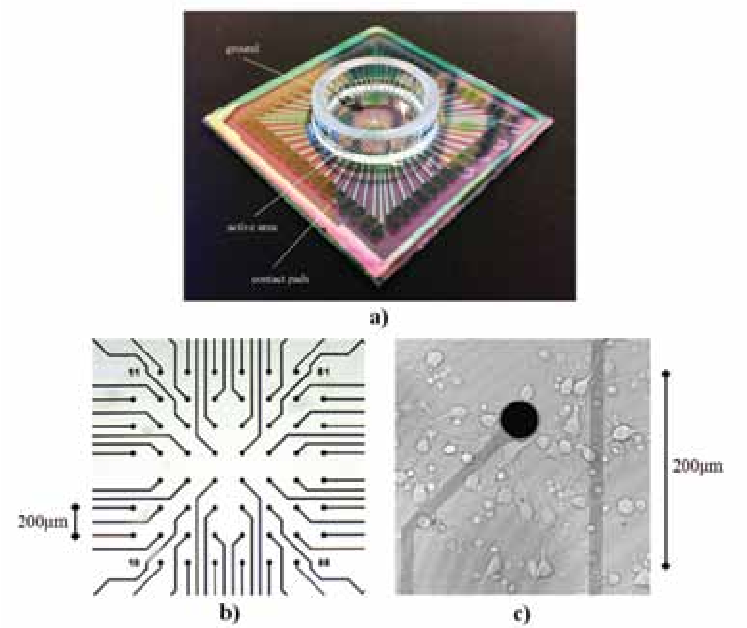

Figure 1. a) An MEA showing the electrodes b) Electrodes in the centre of the MEA seen under an optical microscope c) An MEA at x40 magnification, showing neurons in close proximity to an electrode.

Electrically-evoked responses in the culture are coupled to the physical robot (Warwick et. al., 2010). Sensory data fed back from the robot is delivered to the culture, thereby closing the robot-culture loop.

An initial neuronal pathway is identified by searching for relationships between pairs of electrodes. This is employed to control the robot body –

for example if the sonar sensor is active and we wish the robot to turn away from the object being located.

The robot moves forward until it reaches a wall, at which point the sonar value decreases below a threshold, triggering a stimulating pulse. The robot turns whenever activity is registered on the response electrode. From a neurological perspective it is also interesting to speculate why there is activity on the response electrode when no stimulating pulse has been applied.

The cultured network acts as the decision making entity within the feedback loop. The robot improves its performance over time in the sense that neuronal pathways that bring about a satisfactory action strengthen though the process of being habitually performed. Learning by reinforcement – rewarding good actions and punishing bad is an ongoing research effort.

Experiment 2: Issues

It has been shown that a robot can successfully have a biological brain to make its 'decisions'. The 100,000 neuron size is due to present day limitations, 3 dimensional structures are being investigated. Increasing to 3 dimensions realises a figure of 30 million neurons – not yet the 100 billion neurons of a human brain, but similar to many animals.

The range of sensory input is being expanded to include audio and visual. Such stimulation will have an effect on culture development. The physical robot body can take on different forms - it could be a two legged robot.

The nature of the neurons may also be diversified. At present rat neurons are employed, however human neurons are also being cultured, allowing for the possibility of a creature with a human neuron brain. If this brain consists of billions of neurons, ethical questions will need to be asked (Warwick, 2010).

If the creature has a similar number of human neurons to a human - should it have similar rights to humans?

Is the creature a conscious living being as some philosophers (Searle, 1997) argue?

At present I can simply switch off the robot's life, would that be OK for our creature?

Would our creature be able to vote in elections? If not, why not, when we allow many humans with fewer human brain cells to vote?

Would such creatures do things against humans? With a robot body they may have a wider sensory input and more physical abilities than humans.

What if our creature had more human neurons than a typical human brain – would they make all future decisions rather than humans?

Experiment 3: Deep Brain Stimulation

A steadily growing number of brain computer interfaces are being employed for research purposes or for standard medical procedures.

The number of Parkinson's disease (PD) patients is increasing rapidly as life expectancies increase. For decades researchers have exerted considerable effort to understand more about the disease and to find methods to successfully limit its symptoms (Pinter et. al., 1999), which are most commonly periodic muscle tremor and/or rigidity.

One treatment by means of Deep Brain Stimulation became possible with electrode technology in the late-1980s. From then, many neurosurgeons have moved to implanting neurostimulators connected to electrodes positioned in the thalamus or sub-thalamus.

The technique utilizes a continuous current simulation resulting in battery replacement every 24 months. The cost, the surgery and the trauma of this repetitive surgery limits the patients who can benefit, particularly those who are frail or poor.

The obvious solution, remote inductive recharging has problems such as the size of passive coil to be implanted and chemical discharges in the body. Another solution to prolong the battery life is to improve battery technology – but at an affordable price, this is not on the horizon.

Ongoing research is aimed at developing an 'intelligent' stimulator (Pan et. al., 2007; Wu et. al., 2010). The aim is to produce warning signals before the tremor starts so that the stimulator only needs to generate stimulation signals occasionally instead of continuously.

Artificial neural networks have been applied and have been shown to successfully provide tremor onset prediction. Data input to the network is provided by the measured electrical Local Field Potentials obtained via the deep brain electrodes. The network is trained to recognise the nature of electrical activity deep in the human brain and to predict the subsequent tremor onset outcome. In this way the device could be 'intelligent' when the stimulation is triggered by the neural network output.

Experiment 3: Issues

Deep brain implants can have a broader portfolio in terms of their effects within the human brain. Implantations are forging ahead with little consideration given to the general technical, biological and ethical issues that pervade. It is perhaps time that such issues were given an airing.

The same physical stimulator that is used for the treatment of Parkinson's Disease is also employed for cases of Tourette's Syndrome, Epilepsy and Clinical Depression. Long term modifications of brain organisation can occur in each case, resulting in distinct emotional changes.

If an individual with such a stimulator implanted in their brain was to murder another human and then claim it was not their fault – who would be to blame? The individual? If a stray radio signal had caused the problem could it be the person broadcasting, maybe a celebrity? Perhaps it is the surgeon who put the implant in place, or maybe a researcher who worked on the device 10 years ago?

Now 'intelligent' deep brain stimulators are being designed (Pan et. al., 2007). The computer's job is to out think the human brain and to stop it doing what it normally wants to do. The potential for this system to be applied for a broad spectrum of different uses is enormous – maybe to assist slimming or even to control a spouse!

Experiment 4: General Purpose Brain Implant

With brain-computer interfaces the therapy/enhancement situation is complex. It is possible for those who have suffered an amputation or have a spinal injury to regain control of devices via their (functioning) neural signals (Donoghue et. al., 2004) and stroke patients can be given limited control of their surroundings.

Even with these cases the situation is not simple, as each individual is given abilities that no normal human has – the ability to move a cursor around on a computer screen from neural signals alone (Kennedy et. al., 2004).

Some of the most impressive human research to date has been carried out using the micro-electrode array (Figure 2). Human tests are at present limited to two studies. In the second of these the array was employed in a recording only role as part of the 'Braingate' system. Activity from neurons monitored by the electrodes was decoded to enable an individual to position a cursor on a computer screen, using neural signals combined with visual feedback. The first use of the microelectrode array has though broader implications which extend the capabilities of humans.

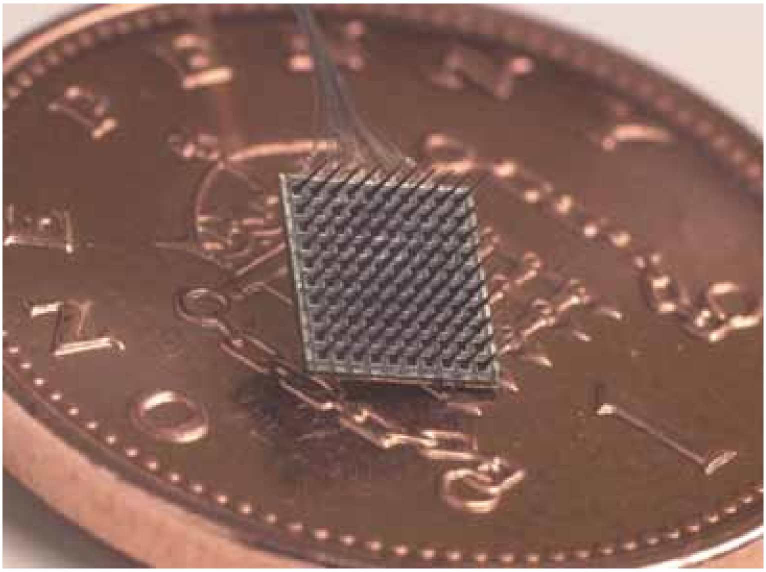

Figure 2. A 100 electrode, 4X4mm Microelectrode Array, shown on a 1 pence piece

The main issue is interfacing the human motor and sensory channels with technology in an effective, bi-directional way. A human so connected can potentially benefit from some of the advantages of artificial intelligence. For example rapid and accurate mathematical abilities in terms of 'number crunching', a high speed internet knowledge base and accurate long term memory. Additionally humans have only five senses, whereas machines also offer such as infra-red, ultraviolet and sonar signals. Humans are limited in that they can only understand the world around them as a three dimensional perception, whereas computers can deal with hundreds of dimensions.

Importantly, human communication, involving transferring signals from one brain to another via a mechanical slow and error prone technique (speech), is so poor as to be embarrassing in terms of speed and precision. Connecting a human brain, by means of an implant, with a network opens up the advantages of machine intelligence, communication and sensing to the individual.

In the first study of its kind, the micro-electrode array was implanted into the median nerves of a healthy human (me) during two hours of neurosurgery to test bidirectional functionality. A stimulation current directly into the nervous system allowed information to be sensed, while control signals were decoded from neural activity (Warwick et. al., 2003). Experimental trials were successfully concluded (Warwick et. al., 2004):

1. Extra sensory (sonar) input was implemented.
2. Control of a robotic hand across the internet was achieved, with feedback from the robot fingertips as neural stimulation for a sense of force (between Columbia University, New York and Reading University).
3. Telegraphic communication between the nervous systems of two humans (my wife) was performed.
4. A wheelchair was driven around by means of neural signals.
5. The color of jewelry was changed as a result of neural signals.

In these cases it could be regarded that the trial proved useful for therapeutic reasons, e.g. the sonar sense for an individual who is blind. However each trial can also be seen as enhancement beyond the human norm. The author, in carrying out this experimentation, specifically wished to investigate practical enhancement possibilities (Warwick et. al., 2003; Warwick et. al., 2004).

Experiment 4: Issues

To get the go ahead for an implantation in each case requires ethical approval from the local hospital authority and also approval from the ethics committee of the establishment involved. Interestingly no general ethical clearance is needed from any societal body.

Should it be possible for surgeons to place implants to make an individual happy, sad or sexually excited? If it is acceptable for a person who is blind to receive an implant for extra sensory input, why cannot everyone have such an implant? Should we develop implants that allow for brain enhancements when it may lead to non-implanted humans becoming subservient? Conversely if individuals wish to have technical abilities beyond the human norm, why should a 'stick in the mud' person be able to stop them?

Conclusions

We have looked at different experiments in which humans or animals merge with technology – thereby throwing up social considerations as well as technical issues. Actual practical experimentation results have been reported, rather than merely theoretical concepts.

In Experiment Number one the main issue was tracking and monitoring. Should such technology be available for parents to be sure their children are safe by knowing where they are at any time? What rights do the children themselves have? Should the same technology be used to monitor the movements of prisoners? Should it be employed to track the whereabouts of those suffering from dementia?

Experiment Number two raised the question of robots with biological brains – ultimately perhaps human brains. Should such a robot be given rights of some kind? If one was switched off would this be deemed as cruelty to robots? Should such research forge ahead regardless? Before long we will have robots with brains made up of human neurons that have the same sort of capabilities as those of the human brain – is this OK?

Experiment Number three looked at some of the ethical issues raised by seemingly therapeutic implants such as those used for the treatment of Parkinson Disease. Not only does the present implant throw up possible problems concerning responsibility if a malfunction occurs but when an intelligent, predictive implant is employed should this be acceptable, even for therapeutic reasons, when a computer brain is outwitting a human brain and stopping it doing what it naturally wants to do? If you cannot do what your own brain wants you to do, then what?

Finally Experiment Number four looked at the potential for human enhancement. Already extra-sensory input has been scientifically achieved, extending the nervous system over the internet and a basic form of thought communication. If many humans upgrade and become part machine (Cyborgs) themselves, what would be wrong with that? If ordinary (non-implanted) humans are left behind as some kind of sub-species what is the problem? If you could be enhanced, would you have any problem with it?

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3

Norman Borlaug's Legacy

Clive James

This paper aims to share some personal insights about the late Norman Borlaug that will reveal something about the man behind the public face. He had three principal values that served him well throughout his life: hard work; honesty; and the genes for ingenuity and perseverance. He was awarded the Nobel Peace Prize in 1970, for saving up to one thousand million people from hunger, as a result of the Green Revolution in wheat, which he championed. In his continuing quest for food security and poverty alleviation, he became the greatest advocate for genetically modified, GM, crops also known as biotech crops. He earnestly believed that the benefits and safety of plant biotechnology had been proven and that they could, like the Green Revolution, help meet the growing demand for food production while preserving our environment for future generations.

Introduction

I had the great privilege of working closely for 30 years with Norman Borlaug (born 25 March 1914, died 12 September 2009) who liked to be known as 'Norm', to his friends. The first 10 years was when I was Deputy Director General at CIMMYT in Mexico, in the 1980s. The last 20 years was when he was active as the first patron of ISAAA, an organization that I founded about 20 years ago whose mission is to share knowledge about biotech/GM crops and facilitate their transfer to resource-poor farmers in developing countries. ISAAA's philosophy is to share knowledge on biotech crops freely with global society, whilst respecting the rights of society to make decisions based on that knowledge. It is an equitable way of sharing knowledge, which is a noble goal in itself. This paper aims to share some personal insights about Norm that will reveal something about the man behind the public face, and pose the question, 'what was it about Borlaug that made him unique'? I think we can all agree that he was indeed unique – a gentleman and a scholar.

He was a son of the soil from Iowa - a farm boy. You can take the boy out of the farm but you can never take the farm out of the boy. He had three principal values:

1. Hard work, which he learnt from an early age on the family farm in Cresco, Iowa.
2. Honesty – he always told the truth.
3. He had two very important genes—they were stacked just like the biotech crops of today—one gene was for ingenuity, and probably even more important, the other gene was for perseverance.

These three attributes served him well right throughout his life.

His contribution to Humanity

There were several events in Norm's life that were of major significance. An important event happened early on during the time he was pursuing studies in forestry in Minnesota when he met an individual on campus who would reshape his life. That individual was Professor E. C. Stakman (1885-1979), Head of the Department of plant pathology in Minnesota. Stakman, known as 'Stak' to his friends, was a fellow plant pathologist whom I also had the pleasure of knowing for over a decade. Stakman was a giant in his field of plant pathology, a humanitarian, an intellectual and an accomplished linguist who spoke several languages. It did not take long for Stak to convince Norm to give up his studies in forestry and pursue a PhD in plant pathology with Stakman. Interestingly, Stakman had earlier convinced, in a similar manner, Dr. George Harrar (1906–1982) to pursue a PhD with him in plant pathology. Harrar was later appointed the first Director of the Rockefeller Program in Mexico (1942–1952) and was Norm's first boss in Mexico. Harrar eventually became the President of the Rockefeller Foundation itself in New York (1961–1972). It transpired that Stakman's role in selecting and influencing Harrar and Borlaug, as well as being instrumental in the establishment of the Rockefeller Foundation program in Mexico was cardinal. This was due to the fact that Stakman was a confidant of the Rockefeller Foundation and a member of the eminent three-man mission (Stakman, Mangelsdorf and Bradfield), which advised the Foundation on its future agricultural program in Mexico. In 1941 when the Rockefeller Foundation established its first program in Mexico Stak opined that the first priority of the 'Office of Special Studies ' was to establish itself as a center of excellence in the principal food crops—maize, beans, wheat and potatoes—a far-sighted vision in 1941. The 'Office of Special Studies' was the precursor to the current CIMMYT program in Mexico.

Stakman and Borlaug, who were both plant pathologists, shared one passion: breeding resistance to stem rust of wheat, which had destroyed wheat crops globally since biblical times. So, Stakman, right from that very beginning, played a very important role in Norm's life. Norm joined the program in Mexico in 1944 as a pathologist for all the crops but after about a year was assigned to lead the wheat program. It is intriguing to pose the question: Had Norm been assigned to the maize program (which was the first crop program to be established in 1941) instead of the wheat program, how this would have changed the course of history of maize and wheat development in the Rockefeller Foundation program in Mexico and the world? Nobody can answer that question now, but it is notable that in the latter part of his career Norm became increasingly interested in maize as a crop, first working on quality protein maize, and secondly his involvement with maize as a principal crop in Africa in the Sasakawa initiated Global 2000 program.

The first picture (Figure 1) shows Norm with his winning smile. He started his second career in Texas A & M when he was 70 years young—not old!!! When students were asked: who is your favorite lecturer? The answer was: Borlaug. Why? Two reasons—First, he always told the truth and second, if you look deep into his eyes, you know that he believes 100% in what he is saying.

Norm's first success with the improved semi-dwarf wheats of the Green Revolution was in Mexico. Three principal elements underpinned their success:

1. First, the new semi dwarf wheats were very responsive to the external inputs of higher nitrogen levels and to an adequate supply of water, through irrigation

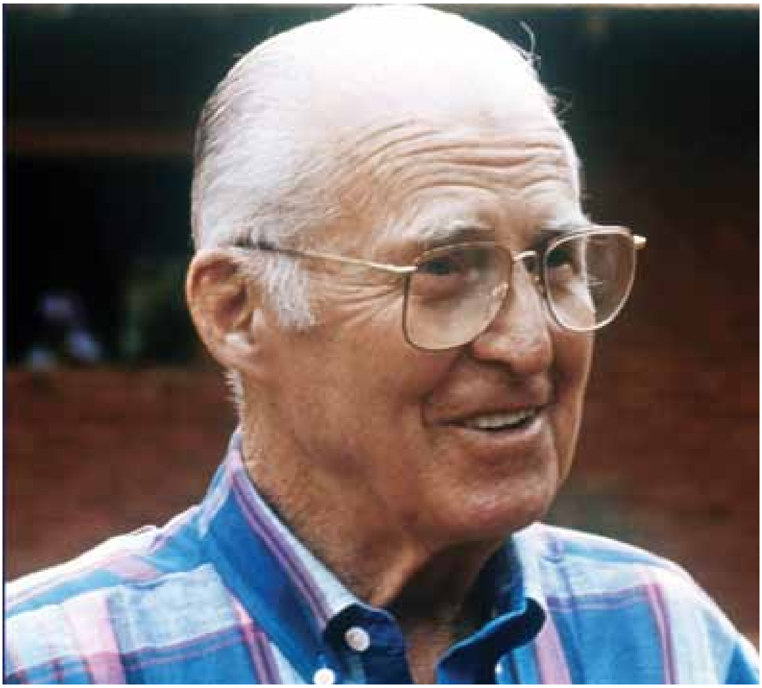

Figure 1. Norman Borlaug Photo

2. Second, the successful incorporation of stem rust resistance was a prerequisite to success, and it is notable that one of the varieties he used to incorporate resistance was a variety called HOPE.
3. Third, the new improved wheats, developed in a shuttle-breeding program between Toluca and Obregon (10 degrees of latitude apart) were day length insensitive, broadly adapted agronomic ally, and thus the wheat germplasm was transferable to different regions of the world, including the important populous continent of Asia.

Remarkably, in only 12 years, 1944 to 1956, Borlaug increased yield productivity of wheat in Mexico by up to 500%, – he transformed Mexico from a significant importer into a modest exporter of wheat.

Having succeeded in Mexico Borlaug and the Rockefeller Foundation started the international program in Mexico and Asia respectively around 1956. It featured an international seed testing/exchange program and importantly a training program which catered to hundreds of the best young wheat scientists from the developing countries of the world – without these two features the wheat green revolution would not have happened. Borlaug understood the potential of the high yielding Mexican wheats that were transferred to Asia. He also understood that in order to ensure sustainabilty you had to invest in people, invest in human capital, through training programs. Mirroring his success in Mexico he brought hope to Asia in countries like India and Pakistan, where, by the mid 1960s, yields of the semi-dwarf wheats were up to 300% higher than the conventional varieties.

Norm became an icon in agriculture following the wheat green revolution, in Asia in particular. This was at the very time that famine stalked Asia, and some people were predicting that countries like India would not survive. It was an age of doom and gloom, but with political will and scientific support, Borlaug's partnerships with fellow scientists such as Dr. Swaminathan in India, resulted in success, and he was able to transform difficult situations into exciting new opportunities – his ingenuity and persistence were omnipotent, and eventually this led to the Nobel Peace Prize in 1970, for saving up to billion people from hunger. In his obituary in the *Wall Street* Journal, it was opined that Norman Borlaug might be the most famous American of the 20th century and that it was a tragedy that more Americans did not know his name – it posed the challenge 'who else can come even close to save billion people?'

The citation by the 1970 Nobel Peace Prize committee is noteworthy.

'Borlaug, more than any other single person of this age has helped to provide bread for a hungry world. We have made this choice in the hope that providing bread will also give the world peace. He has helped to create a new food situation in the world and has turned pessimism into optimism in the dramatic race between population explosion and our production of food.'

In virtually every presentation that I heard Norm deliver he always talked about the 'population monster', and the need to keep global population under control. For those of you who have not read his acceptance speech of the Nobel Peace Prize, of 10 December 1970, I commend it to you. His speech clearly exhibits the enormous breadth of Norm's interests, which he entitled 'The Green Revolution, Peace and Humanity' (Borlaug, 1970). Norm was not just an agronomist he was a true humanitarian. Norm's acceptance speech for the Nobel Peace Prize that he delivered 40 years ago had two important hallmarks. First, if you read the speech today, it is just as applicable now as it was 40 years ago. In fact, today we have even a bigger challenge because we have to double food production sustainably on less resources, with water being particularly important, in the face of more frequent and more severe droughts associated with climate change. Secondly, even though I have read the acceptance speech at least 10 times, every time I read it I find something new. Norm has squirreled some nuggets of wisdom in every nook and cranny in his acceptance speech for the Nobel Peace Prize, which he composed with divine devotion – his acceptance speech of 40 years ago is evergreen.

Let us have a little deeper into the strategy that Norm implemented that made it unique? How can we capture Norm's legacy for posterity? I would like to propose that Norm's strategy could be summarized in the Trilogy of the Three Ps.

1. Productivity: the first P is for Productivity. Norm Borlaug had a laser-like focus on increasing productivity (kilograms of grain per hectare). His leadership qualities allowed him to unify the goal of his multidisciplinary team on wheat productivity. Norm was not one to pass the buck – he was similar to President Truman who had a sign on his desk that said 'The buck stops here'. Norm insisted that the success or failure of his semi-dwarf wheat program be judged on the productivity of wheat in farmer fields not productivity of wheat plots in the experimental station.
2. People: the second P is for People. Even though Norman Borlaug was in love with wheat germplasm, – he thought about it 24 hours of the day, and knew it better than anybody else in the world. However, Norm understood that there was one germplasm that was even more important than wheat germplasm – and what is that? It is human germplasm. He knew that you first needed to shape human germplasm, through training, in order to shape wheat germplasm. So the second P is for People, investment in human germplasm and human capital. Importantly, he recognized this from the very beginning of the international program in 1956 and embarked on a training program in Mexico for carefully selected young wheat scientists from the developing countries destined to become the leaders of tomorrow.
3. Poverty: the third P is for Poverty. Unlike most agronomists Norm's eyes were always focused over the horizon, not just on the horizon, and he never forgot that his mission in life was for an ultimate humanitarian cause, Poverty alleviation. I think we often forget that poverty is the most pervasive pollutant in the world today – it pollutes the lives of over a billion people, and for Norm, who had personally experienced the great depression of the 1930s, poverty was

morally unacceptable. I believe that if we can use modern crop biotechnology to alleviate poverty then that is the zenith of success.

What more can we say? Can we find another P for Norm's strategy that will allow us to transform the trilogy into a quadrilogy ? I believe so.

4. Peace: the fourth P is for Peace. In virtually every speech that I heard Norm deliver he would say that you cannot build peace on empty stomachs, and that is a truism. In fact, it was Sir Boyd Orr, the first Director General of FAO, who actually coined that phrase, but it was Norman Borlaug who gave the phrase meaning – we have exactly the same challenge today in a world that is already rife with inequity and unrest.

So, the four Ps, summed up in the simple quadrilogy – Productivity, People, Poverty and Peace summarizes Norm's evergreen strategy for feeding the world of tomorrow. Remarkably, the four Ps are as applicable today as when Norm practiced them more than fifty years ago – Norm always practiced what he preached, and preached what he practiced. Thus, Norm's legacy can serve as the blue print, that will hopefully allow us to feed the world of 2050 and beyond, when mother Earth, for the first time ever, will carry more than 9 billion people, of which more than 90% will reside or survive in the developing countries of Asia, Africa and Latin America.

After gaining fame as a Nobel Peace Laureate Norm became a mentor, not to hundreds, not to thousands, but to millions of people, particularly followers from the developing world. In the second picture (Figure 2) Norm is with some young African farm boys to whom he was a mentor. The young African farm boys, who will become the African farmers of tomorrow, are smiling because of Norm's infectious smile. Remember that Norm was a pathologist, he knew a great deal about epidemiology, and he knew the value of an infectious smile – like most farmers, Norm was also a great storyteller and was always at his best in wheat fields with young people.

However, the intriguing question is—if Norm was a mentor to millions, who was Norm's mentor? There was one man who stands out—it was Stakman. Norm compared Stakman to Socrates but he was too modest to take the analogy further. However, those of you who are Greek scholars will know that Socrates' most gifted pupil and prodigal son was Plato. Thus, what Plato was to Socrates, Borlaug was to Stakman. In Athens in 350 BC Socrates and Plato used to walk in the olive groves of the Academy, the first University in the world, and they used to discuss the great challenges

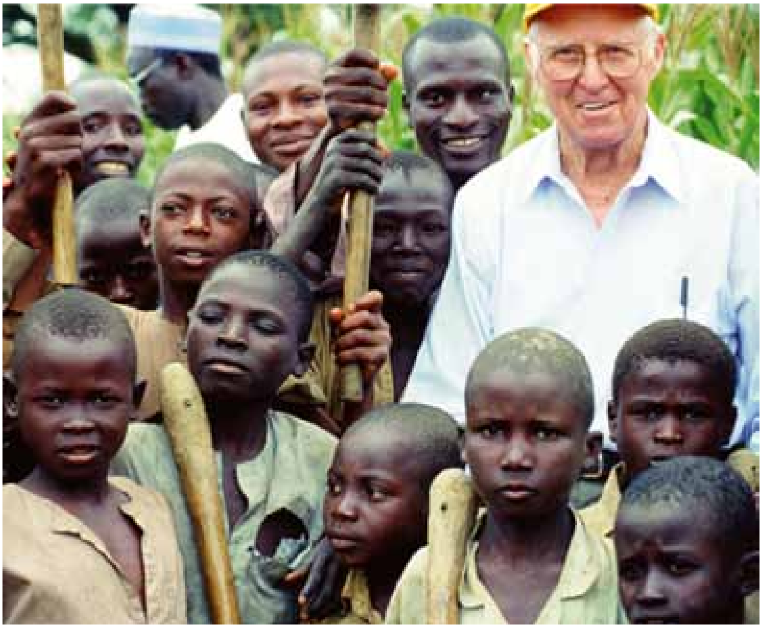

Figure 2. Norm with happy, smiling African farm boys

facing Athens. In fact, in 350 BC Plato came to the magnificent library in Alexandria, so the institution has a great place in history and a rich legacy. It was 350 BC when Socrates and Plato walked in the olive groves of Athens. If we wind the clock forward 2,350 years, we find a parallel—two gentlemen walked together in Minnesota—they were not Socrates and Plato they were Stakman and Borlaug. They did not walk in the olive groves, because there aren't any in Minnesota, but in the wheat fields of Minnesota, and their mutual passion was to breed wheat resistant to stem rust. Borlaug made their mutual dream come true, and indeed the Green Revolution would never have happened had Borlaug not been able to incorporate stem rust resistance in the semi dwarf Mexican wheats, which underpinned the success of the Green Revolution.

His advocacy of genetically modified/biotech crops

When Norman Borlaug passed away on 12 September 2009, he was not 95 years old, he was 95 years young!!. He always had a young mind, a mind that allowed him to synthesize different experiences and create something novel. There is no Nobel Food Prize, (he received the Nobel Peace Prize), so in 1988, he founded the World Food Prize, because he earnestly believed that the critical importance of 'food security 'deserved to be highlighted for global society and assigned the highest prominence on the global stage. In 1990, he accepted my invitation to become the First Patron of ISAAA. It is notable that although Norm had been awarded the Nobel Peace Prize for conventional crop technology he was also the greatest and most credible advocate for biotech/GM crops, having saved 1 billion people from hunger. He was a fierce fighter for Science, Technology, and Innovation, all pursued in order to alleviate Poverty and Hunger. Today, over a billion people suffer from hunger and 24 thousand people a day die from hunger – this is despite the fact that we, as a global community, have pledged that we will cut poverty by 50% by 2015, the Millennium Development Goal (MDG) Year. Consistent with Norm's view of crop biotechnology I also fervently believe that the best of conventional crop technology combined with the best of crop biotechnology can make an enormous contribution to food security and the alleviation of poverty and hunger. In my view this will be the most important contribution of crop biotechnology. Indeed if we fail to alleviate hunger and poverty, we risk a breach of global security, and now is the time to act.

The graph (Figure 3) shows the adoption of biotech crops on a global basis from the genesis of commercialization in 1996, to 2009 (James,

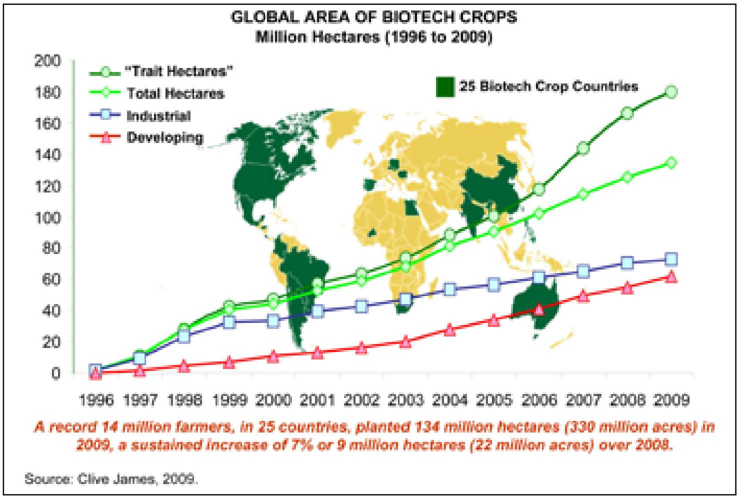

Figure 3. Global Area of Biotech Crops (Million Hectares 1996-2009)

2009). Remarkably, there has been a 80-fold increase, from 1.7 million hectares in 1996 to 134 million hectares in 2009; this makes biotech crops the fastest adopted crop technology in the recent history of agriculture. The high rates of adoption is due to the confidence and trust of millions of farmers who have made 85 million independent decisions in 25 countries over a 14-year period to plant and replant biotech crops, because of the multiple and significant benefits they offer. Some of the groups opposed to biotech crops claim that biotech crops have done nothing for nobody—if they are right, then 85 million decisions by farmers are all wrong—I will leave you decide who may be right.

Biotech crops have delivered handsome benefits; increases in production valued at $52 billion over the 13-year period 1996 to 2008: a decrease in pesticides of 350 million kg which is about an 8% saving: and they have also made a contribution to welfare benefits. For example, in India compared with villages using conventional cotton, women in the Bt cotton villages who benefit from higher income from Bt cotton can afford more medical assistance with births at home (which is the traditional way); similarly a higher percentage of the children in Bt cotton villages go to school, and a higher percentage of them get vaccinated. These experiences with biotech crops excited Norm, since he viewed it as a follow-up second revolution to the Green Revolution that saved up to a billion lives.

Conclusion

To close, I would like to share with you the views of Norm on biotech crops—these are the views of the architect of the Green Revolution—the man who knew more about crop technology and feeding the world than any other person simply, because he had done it – the proverb says reading is learning, seeing is believing, but doing is knowing. Borlaug's counsel on biotechnology is captured in the following eloquent quote from him.

'Over the past decade, we have been witnessing the success of plant biotechnology. This technology is helping farmers throughout the world produce higher yield, while reducing pesticide use and soil erosion. The benefits and safety of biotechnology have been proven over the past decade in countries with more than half of the world's population.'

The next sentence is the most important:

> 'What we need is courage by the leaders of those countries where farmers still have no choice but to use older and less effective methods. The green revolution and now plant biotechnology are helping meet the growing demand for food production, while preserving our environment for future generations.'

His final mission in 2009

In 1999, his old enemy, stem rust of wheat, recurred in Uganda - a virulent strain that is called UG99 (short for Uganda 1999). He recognized the gravity of the situation and decided that urgent action was needed. Borlaug secured funding support from the Bill and Melinda Gates Foundation to use the best technology to protect the wheat of the world from UG 99. In the fifty years since Borlaug conquered stem rust, new scientific tools have become available to fight against this deadly disease. Poignantly, his last visit to his beloved Yaqui Valley in Mexico, where he had successfully toiled to incorporate resistance to his old enemy, stem rust of wheat, 50 years ago, was to review the progress being made in the Gates Foundation UG 99 project. In a final moving address from his wheelchair, he spoke elegantly, and eloquently of the progress being made, confident that once again, science would prevail over his old enemy, stem rust of wheat.

Borlaug was an icon, and a leader to the poor farmers of the world; he placed great trust in poor farmers and understood that they are the best observers and judges of crop technology when deployed in the field – in fact, his very last words were 'take it to the farmer'. So, how can we capture Norm's legacy for posterity? As scientists we have limitations in capturing the jewels of the past and passing them on to the next generation. It is the poets that are best able to do this in few words. The closing five lines of free verse is an attempt to capture his great legacy for posterity:

> He cared, more than others thought wise
> He dreamed, more than others thought real
> He risked, more than others thought safe
> And he expected, and usually achieved,
> what others thought impossible
> God bless his soul.

Acknowledgements

I thank Dr Malcolm Elliott, the organizer of the session to honor Norman Borlaug at BioVisionAlexandria 2010, Egypt, and Dr Ismail Serageldin, Director, Bibliotheca Alexandrina for the invitation to contribute this chapter as a legacy to Norm, my mentor and friend.

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Biotechnology's Philosophical Challenge

Werner Christie

Summary

There are many reasons to be impressed by recent leaps in life science and the new understanding of the mechanisms of life. Research in biotechnology and genomics in particular saw its biggest breakthrough with the completion of the Human Genome Project in 2001 and the sequencing of a host other genomes since then. We still have to admit, however, that biotechnology has not yet met the huge expectations proclaimed a decade ago. The impact is still limited, especially for less privileged people in developing countries, but even for most end users in the more affluent part of the world such as patients and food consumers. This paper explores the current intellectual and real world political context of the biotech revolution. Its aim is to try to reconsider our direction of development and shift the focus areas to maximise cost effective impacts for those who need it most.

Current Contexts for Biotechnology

Biotechnology will potentially influence the economic, ecological and political realities of the world. But it is also itself dependent on these. Let us therefore first consider how the global economic, ecological and political backdrop for the biotechnological revolution shapes its possibilities to make impact the improvement of livelihood for people.

Economic crisis

We have after the financial collapse in 2008, been through a global economical crisis. It was also a collapse of the current economic paradigms and the idea of the economy as a scientific discipline. It did not only involve the financial segment of the economy where it was initiated, but also heavily impacted productive realms of the economy. It demonstrates a point that Michel Foucault described in his deliberations about 'Gouvernmentalite': The most dangerous of modern power structures is the power of ruling ideas. The economic crisis tore down financial institutions in spite of the fact that these are the very same people and institutions who should have been the first to see the writing on the wall, understand its consequences and correct the course.

Mindset and ideology in the dominating financial institutions, in the political communities and among the regulators was the main cause of the crisis. Ironically, those paying the price for the intellectual negligence of those at the top are primarily people at the lower end of the ladder; those being evicted from their homes and jobs and struggling to pay for daily necessities. The lessons learnt have been summed up by the economist Frank Ackerman: '… the market may be the engine of a socially directed economy, indispensable for forward motion. There are limits, however, for its capabilities: It cannot change its own flat tyres, and if we let it steer, we are sure to hit the wall again.'

In addition to the obvious setbacks for long-term investments in biotechnology, the financial crisis also illuminates the fact that market incentives do not necessarily serve the basic needs of the least privileged; but that they do serve the needs for profit by those controlling capital.

Ecological crisis

In parallel we have a rapidly escalating global ecological crisis produced by the extractive mindset of the productive segment of the economy: The external costs for emitting pollutants into the commons like air, water and landfills are not calculated as a cost to be covered by the polluter, but as a price to be paid or tolerated by the community. Climate change is now the dominating threat looming over the fragile ecological balance on our vulnerable planet. In this case we all are the victims, but again the less privileged are paying the highest price. Our understanding of biological systems large or small and their interconnectedness are obviously yet very limited, and we tend to approach them with an inappropriate and simplified technocratic mindset.

Equity and population crisis

Even more dramatic than global financial and ecological conditions is the crisis of equity within countries and between countries. More than 1.3 billion still live below the poverty line. On top of this we know that the world's population may rise by an estimated 2.5 billion over the next generation before it begins to plateau. This population increase will come mostly in the already under-privileged countries. These new world citizens will also need food, shelter, health care, education and employment. It is already a huge challenge to provide enough food and basic services to these countries and the broad potential benefits of biotechnology have not yet reached them.

These are the unprecedented and potentially disastrous challenges for the ecological system and for livelihoods in our planet, caused by the only species that also has the possibility to reverse them. I believe these contextual conditions compel us to reconsider how biotechnology can play a more productive role for the benefit of the least privileged.

The Intellectual Challenges of the current Crises

The intellectual paradigms driving developments in philosophy, science and economic growth since the Renaissance has been that of reductionist analysis and a linear understanding of cause and effects. Core to this thinking is the idea that the whole can be studied and understood as the sum of its parts, and that cause and effect is a linear relationship.

Newer insights and concepts in biology, ecology and economics make it clear to us that a system is more than the sum of its parts, and that system effects can be based on complex feedback processes influenced by a number of factors. Systems needs broader concepts to be fully understood, and manipulating them to create specific results can be extremely complicated.[4]

The paradigm of systems and systems analysis

Healthcare is probably one of the biggest such ventures of mankind. The World Health Organization in a recent paper accordingly promoting a systems paradigm for analysis and political understanding of health care systems. This approach emphasizes that systems are dynamic, not static;

that they are a cause in themselves not only effects, and that they are self-organizing, nonlinear, constantly changing, history dependent and tightly linked, often counterintuitive, governed by feedback and can be resistant to change.

Using this paradigm of systems thinking, we can reconsider the context and future prospects for the impact of biotechnology. We then see that the above mentioned predicaments challenging the world today are closely interlinked: The economy impacts directly both the ecology and the equity of the world. Ecological change threatens to undermine many segments of the economy and deepens the equity crisis. Poor people that do not get health care and education have less to contribute to the economy. Moreover, explosive population growth exacerbates these problems to a dramatic scale.

Considerations for biotechnology

Considering how technology and biotechnology specifically can contribute to sustainable development and sustainable livelihoods, we may also have to reconsider our current approaches to technology development—including in biotechnology. We may need to recognize that those most in need will have the least resources available. Technology will have to be simple, cheap, quick and easy to distribute; applicable on a large scale in difficult contexts.

The main paradigm of biotechnology has, until now been very much based on a Cartesian, linear concept and mindset. For example, we want to sequence and understand the function of individual genes and molecular pathways; we want to manipulate them and thereby create better health, food supply and ecological sustainability. Such a strategy is not at all unreasonable and it needs to be pursued with persistent efforts. However, it is also clear that our simplified understanding of genes only 10 years ago has been through several paradigm shifts since then: A substantial portion of what was considered un-functional 'junk genes' turned out to be important regulatory genes. Short RNA sequences were also proved to have a multitude of independent regulatory functions. A deeper understanding of proteomics and epigenetics made the prospects for a straight forward way from identification of genes to treatment of major disease much less realistic, but enhanced our understanding of organisms as complex feed-back systems.

This rapid sequence of what could be called minor scientific revolutions, gives us reason also to challenge our current mind-set in biotechnology more broadly. My argument in this article is that our current approach to data-mining for drugs leads is unlikely to be sufficient, affordable and quick enough to have sufficient impact to alter the grave consequences of the combined impact on the four main global challenges mentioned before, especially for those with the biggest needs. We need to add other paradigms and strategies as well, based on lower hanging fruits to tap the full potential of biotechnology. Most global health challenges are generic, not genetic. Therefore population strategies are more important than personalized medicine.

We should consider simpler and more straightforward strategies based on the understanding that balances of systems help to push them in a more favorable direction. This can potentially have a bigger, more rapid and substantial impact than complex high-tech biotechnology products based on intensive and expensive, long term basic and applied research.

Among the criteria for an effective and appropriate application of biotechnology for health in low income countries should be the following:

- Realistic analysis regarding potential technology impact
- Technologies should be affordable, accessible, simple, effective, and easy to apply
- Programs should be based on broad systems considerations
- Upstream prevention should be preferred before cures for manifest crisis
- Population based interventions to be preferred before individual treatments
- Technologies should create coping capabilities for people, rather than increase need for health professionals

When looking at the wellbeing of the human organism as a whole from a systemic perspective, we would primarily focus on the relationship of the organism with its environment and its responses to various environmental factors. The most important relationship between organism and its environment is mediated by the intake of various sources of energy and nutrients and the responses these invoke in the organism. This, I would argue, is a more productive and relevant approach to the concept of systems biology. The idea of a personalized medicine is not important for most of the major health needs and epidemics of the world. This is what I mean when I say that most of the common diseases as well as their solutions are generic, not genetic.

We know that many of the major epidemics of the world such as cardiovascular disease, cancers, diabetes/metabolic syndrome as well as infectious diseases have complex genetic components. At the same time they are also mediated through our intake of foods and nutrients as well as our exposure to physical, chemical or biological substances. Accordingly, our strategies to fight them should be searched for in the same domains, also by those trained in biotechnology.

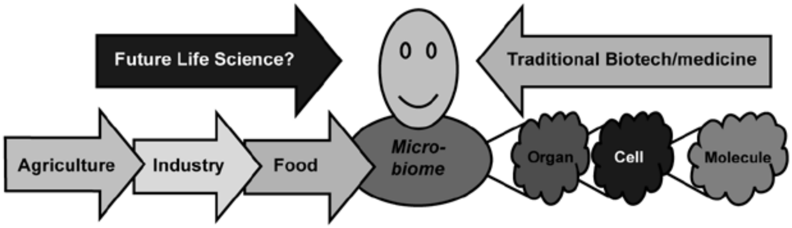

Figure 1. Contrasting Paradigms of Biotechnology

We should focus more on broad scale public health issues related to the interplay of ecological and biological systems like the human organism as well as the benign and harmful effects of the human micro-biome.

Let me briefly exemplify and substantiate such a claim with a couple of promising examples from my own field of knowledge, medicine.

Vitamin D, an evolutionary protective substance

Vitamin D is a substance that can be found in a number of biological organisms and contexts. It has been with us for a long period of evolution, and has apparently defended its ground as an important and useful substance for survival. It has long been recognized as an important micronutrient with well documented effects on both juvenile and post menopausal bone disease.

What is less well known, is that a rapidly growing body of research indicates strong associations between Vitamin D status and a number of other pandemic diseases such as diabetes, multiple sclerosis, some infective diseases and possibly cancers. Given that big segments of the world population both in temperate and more sunny tropical zones seem to have suboptimal physiological levels of Vitamin D, it is estimated that a simple program for improving the Vitamin D status of the population could have huge medical as well as economic benefits, with minimal risks and moderate costs.

Our current need is to be able to further understand the functions of Vitamin D in organisms, and to reveal possible biological mechanisms behind its apparent substantial preventive effects for a number of pandemic diseases. With further specific knowledge and documentation of these effects, simple and cheap preventive programs with potentially huge impact on the health and wellbeing of both rich and poor

Omega 3 fatty acids and their biological impacts

Another example is Omega 3 fatty acids and their well documented effects on eye and brain development in infants, as well as potential benefits for the immune system and protection from diseases such as cancers, cardiovascular disease, rheumatoid arthritis, psychiatric disease etc.

This kind of biotechnology based on the understanding of evolutionary selected beneficial substances and their function in biological systems, may therefore be much more relevant and have a potentially much bigger impact on global health challenges than sophisticated biotechnology and personalized medicine. We should prioritize our research agenda accordingly.

Preventive programs for Vitamin D and Omega 3 deficiency can be as simple as advising more moderate sun exposure, eating more fatty fish, simple fortification of staple foods or individual supplementation, for example by simple and well tried substances like cod liver or plant oils. Biotechnology does not have to be complicated to be effective, and the simpler the technologies are the higher the probability of an effective implementation of programs and broad and substantial effect on people's health.

However, to be able to promote this mode of biotechnology based on comprehensive systems analysis and understanding we need to develop a different research and public health agenda. We may need to change research paradigms, and expand analysis and research methodology into another kind of collaborative research, where basic biology, epidemiology, social sciences and developmental economy is integrated on a much higher level than today. And we need to inform policy makers not only about the future potential of sophisticated biotechnology, but draw their attention to the low hanging fruits of simple biotechnologies ,based on a deeper understanding of the interrelationships of complex systems.

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5

Is Progress the Same as Development?

Biljana Papazov Ammann

What do we need as visionaries: Progress or Development? I ask this question because I am convinced that we need to build a new culture of questioning. We need a culture orienting itself by authentic questions. How can we develop taste and the ability to distinguish between those questions which are cognitive, statement-oriented and those which are authentic, close to life and to people? What is more important: cognizance or decision for action? How can we move between Statements and Questions? Statements reflect the need to understand the world. But they are the result of past experience and are often contained in frameworks which are coined by society. They may even protect old routines which hinder innovation. Questions, in contrast to statements¸ can transform our judgements and prejudices. Questions give birth to energy for new orientation, for a more conscious future. This orientation towards the future, towards vision provokes those choice-questions, and they alone will open the way for an urge to change the world. Visions need people who are free! The quality of freedom is inherent in the question. We must strive for this quality through choice-questions. If we cannot befriend these choice-questions with science, it will disengage from the questioners and will not be human science anymore. Thus we need a new humility of thinking–as it has been wonderfully defined by the German philosopher Heidegger: 'The question is the devoutness of thinking.'

Dialogue

Organizing a meeting with so many participants entails a lot of work and engagement – and it is also expensive. Harnessing the powerful force of this enthusiasm within the organizational work cannot be taken for granted. Evidently our hosts are conscious of the importance of conducting such a dialogue, in which personal relationships, trust and engagement can mature and thus our hope for a better future can take shape and become reality.

I am impressed to be in the community of biologists and to realize the huge amount of knowledge, all those answers on various problems, but my idea is to emphasize the role of producing authentic questions – questions, which are bound to concrete situations. But the aim should be how to put ourselves on the path to wisdom. I agree with Ismail Serageldin in his opening speech that knowledge is not the same as wisdom. Science and related knowledge can only become meaningful if it can detach itself from the status of statements and move towards real human beings and their actual problems.

Vision = resonance between knowledge and wisdom. That means we have to question in every situation the possibility of resonance in order to reach it. This is the reason why I decided to concentrate my contribution on an appeal for a new culture of questioning. I have also tried to define, in my summary, the necessity to differentiate between the various types of knowledge in order to understand and apply them correctly. Often, I will use metaphoric language in order to move more quickly and easily between essential life systems.

In this way, I will divide knowledge into two important groups:

The path of cognition and the path of choice, so that we can challenge the title of our session: 'Rethinking Science and Technology in the 21st Century'.

The Roundabout

We have enormously detailed knowledge concerning the phenomenon of life and a large part of it is available electronically. We have the opportunity to receive fast answers to our questions. We are also innovators, but we are ever less able to make use of them. That is our personal drama!

Metaphorically, we live in a so-to-speak breathtakingly-speedy 'Answer Civilization'

The ancient Egyptian civilization was also an answer culture, only it consisted of a vertical dialogue between 'Heaven' and 'Earth'. In the historical cultural tradition of that time an inspirational outlook existed between questions and the content of knowledge. In today's cultural historical perspective, this is different because inspiration has fallen into disuse and the knowledge content has become dogmatic.

Dialogue has now become horizontal and for that reason even weaker, superficial and often very bureaucratic. Even though science has so much to offer – it is unable to defend itself in public through its own tools. It requires another pair of spectacles to learn to see, in order to comprehend its own shadow side.

The scientific industry of today has a shadow side which one could describe as an 'answer factory'. This answer factory phenomenon is a dangerous phenomenon because it is often misused by the 'protest-industry'. In the end, we are all victims of this as we maneuver ourselves directly into a compulsory growth paradigm.

The 'eco-Stalinists' (the protest-industry) propagate mistrust with regard to scientific research; scientists feel their scientific ethos is damaged and concentrate on providing every possible answer. This is totally unacceptable to the general public, since it requires a specific competence. As a result, the scientists keep to themselves and this unnecessary roundabout dynamic of social life perpetually intensifies. A kind of ping pong game ensues, which allows no pause for reflection or orientation.

Biology, which has as its objective the study of living things, loses focus on its direction and looks for it once more in man-made biology.

Why has this gone so far astray?

It is because of the too-hurried, anachronistically developed answer culture, which has strangled the new question culture and thereby leveled our understanding of life. Answers are ready-prepared before the authentic questions are generated. So an unnatural process is set in motion. Instead of waiting to see which questions are posed and which kind of answers these existential questions are called for in our lives, we allow ourselves to be dominated by the reverse process. We permit ourselves to be led by too hasty answers to too hasty questions e.g. we withdraw ourselves even further from our needs, so that the speed of this roundabout no longer allows the direction or the quality of progress, not to mention the development of fate – individual and collective.

At the 'Darwin Now' Conference in November 2009, I showed a cartoon-type illustration to indicate the difference between 'modernity' and 'post-modernity' over the past 200 years.

The cartoon of Descartes – *I think! Therefore, I am!* And Baudrillard's – *On the contrary, I consume! Therefore, I am!*

Figure 1. Descartes in the Modern time (17–19th century): Cogito ergo sum! I think! Therefore I am! Baudrillard in the Postmodern time (20th century): On the contrary, I consume! Therefore I am! From Powell, J. Postmodernism for Beginners, 1998, p. 48

At that time, when I tried to indicate a way out, a way we could exit from the paths of consumption and loss of direction – and these with the help of a new sensitivity towards art, beginning with the art of listening to the fates life bestows on us, I was interrupted by a young biologist from India with the words, 'Let us not lose any more time. Let's talk about science!'

Science in the Context of Human Fate

Since then, I have questioned myself earnestly. Can a discussion about the essence of science in the context of human fate really be regarded as a waste of time? I then purchased a DVD of a documentary film about the life and death of Francisco Varela. He was a biologist, who awoke an enormous enthusiasm and respect in me and I'm sure I am not his only fan in this room.

The film shows his great and very passionate devotion to biological science, which can seldom be surpassed. He recognized the genius of science and as such admired, loved and defended it. Photos of Francisco Varela

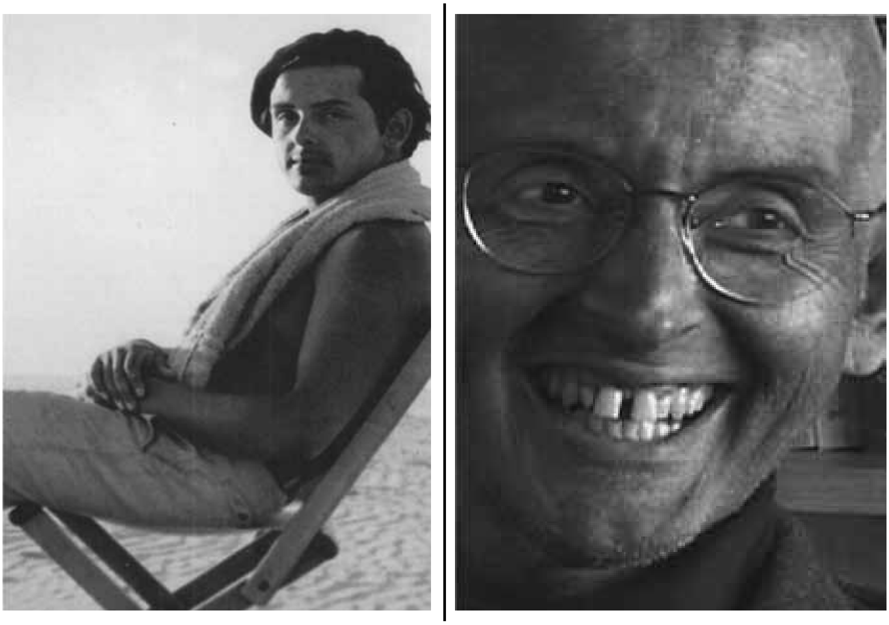

Figure 2. From Francisco Varela DVD Monte Grande Trailer http://www.youtube.com/watch?v=3dzMfDuLRc0 2004

But he also perceived that the naivety of scientists could no longer be tolerated today. His dearest wish was that scientists should learn to keep a question in mind, permitting it to mature and constantly reconsidering it until the answer automatically came of its own accord.

This internal confrontation with questions, until their depth is apparent, is an art – a modern initiation into a new culture, which should follow on from the former answer culture and represent the future. I call it the question culture.

The new question culture or design of the future

The future has an ambivalent character – it can make us afraid and therefore lead us to hide behind so-called 'objectivity' e.g. such as science or bureaucracy into a kind of dead-end or it can inspire us to tolerate its freedom.

In any case, we have the freedom to face problems without fear, because we have the possibility to prepare ourselves for it. Our opportunity lies in the ability to make sense of things, in the ability to constantly re-shape our judgments, or in other words in the dynamic movement of questioning thought.

The energy for the process of opinion-forming springs from one question

However, it depends to a large extent on the depth and quality of the question – how much power it can create, in order to solve the problem. That means that before we can proceed on our way to create a future, we must develop a culture for the formation of authentic questions in advance.

When I try to characterize this culture, this attitude, it is worthwhile to identify a few typical features:

- Questions must arise before the decision model
- The questioning should take place throughout in personal language, the so-called 'I-language', 'me-language' or in the 'first-person science' (F. Varela) so that the conscience and concern are addressed
- Me-language is existential, not short-term, and not superficial, cannot be manipulated, and is not implicit but explicit. This me-language is capable of stimulating the human substance and creating the future because it is the language in which authentic questions bear fruit

The authentic questions are questions to me personally and to those others affected by them.

They are questions of perception and those requiring assistance. They result from two different sources: the perceptive way and the way of choice and these two ways are not interchangeable. The best science is not capable alone to make a choice and the best choice cannot accomplish good without the help of science.

The protest-industry uses exactly this gap, this lack of knowledge, the naivety of the scientists and conquers it in a parasitic way as its own eco-niche.

If one wishes to confront an apparent loss of direction in our society, then another way has to be chosen.

The anti-social accent of productive manpower can be transformed by a new morality – beginning where the ontological question can play a converging role. Only the questions of needy human beings have a converging, focusing meaning with regard to directionless production capacity. When we learn to carefully allow these ontological questions to mature within ourselves, then we have achieved it: we have allowed the dynamic to be stimulated within our own souls and in other groups and thus made a living future possible. We need role models

The seeds of the future are not so easy to locate in the visible world around us, in opposition to the results of perception and the questions generated by them. Future seeds are fragile, just as the essence of living science is fragile and needs to be carefully nurtured.

It is impressive how Francisco Varela perceives himself as a troubadour, who sung his song of love for science again and again at congresses and conferences. It is deeply moving to hear how he describes the curiosity and diligence with which the passionate scientist delights in world discoveries behind the phenomena. This perceptive path is marked by the enthusiasm and admiration for the beauty and depths of life itself.

This way alone does not have the power to bring out the deeper beauty of life on earth, because this power lies in our choice namely our questioning choice.

This permits it to be tied to clarity of thought, through empathy and conscience.

In this sense, I end with the wonderful definition of the German philosopher, Heidegger: 'the question is the piety of thought'.

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6

New Approaches to Scientific Integrity

Joel J Nobel

Introduction

Scientific integrity is a critical issue that impacts the worldwide academic, healthcare, industrial and scientific communities and the public interests they serve. Over the past two decades examples of perversion of research in healthcare has come to public attention, especially in the United States. Examples abound in other nations. The problem is a universal one affecting virtually all industrialized and developing countries and in research in the physical, engineering and biological sciences as well. In those countries with a strong research base distortion of research by lapses in integrity wastes institutional and human resources, distorts social priorities and may cause harm to individuals and environment.

Scientific Values

The value system of scientists has traditionally made the following assumptions:

- Researchers accurately record and report data from their experiments
- Researchers base their conclusions on objective analysis of their data
- Research funding sources have little or no effect on the preceding assumptions
- Researchers are immune to the weaknesses of other mortals such as ego, greed, self-delusion, selfishness and the wish for recognition and social approval

Clearly there are many historical and more than a few contemporaneous examples to the contrary. But because of the strength of belief in these assumptions most academic research institutions have failed to develop and implement effective research review and verification policies and procedures. Part of this gap is caused by the longstanding tradition of academic freedom and the autonomy granted to academic departments and the professoriate.

Scientific Integrity

There are several broad issues that most commonly undermine scientific integrity. One is scientific misconduct and the other is self deception. Both are very damaging to the scientific establishment, society and the fund of human knowledge. Scientific misconduct is intentional and is sufficiently common in healthcare research that the U.S. Government established a formal Office of Research Integrity within its Department of Health and Human Services to deal with the challenge. Its criteria and definitions are noted below.

Scientific Misconduct

Scientific misconduct is usually defined as:

- Fabrication: Making up results and recording or reporting them
- Falsification: Manipulating research materials, equipment or processes or changing or omitting data or results such that the research is not accurately represented in the research record
- Plagiarism: Appropriating of another person's ideas, processes, results or words without giving appropriate credit, including those obtained through confidential review of others' research proposals and manuscripts

In addition:

- Violating ethical standards with human or animal experiments: Failure to obtain informed consent from human subjects, failure to disclosed known detrimental effects to research subjects, failure to house or treat animals in a manner consistent with related regulations
- Ghostwriting: Disguising authorship and attributing it to a scientific researcher when the paper was actually written by an interested party such as a drug company
- False assignment of authorship: Attributing authorship inappropriately to one or more individuals who did not actually contribute significantly to a scientific

study or preparation of related papers. This is common practice in academic departments. There several reasons for this behavior. It increases the probability of acceptance by a journal by adding the name(s) of one or more better known scientists. It allows more senior individuals to take credit for the work of a junior researcher who is not in a position to object and it builds the list of scientific papers allegedly generated by senior researchers and department heads. It also has the effect of placing the quantity of published papers on the same or a higher level than the quality of papers. It addition, it reinforces the ego boosting master-slave relationship that underlies the professor-graduate student connection

- Suppression: Failure to publish significant findings because the results are contrary to the ideological or financial interests of the researcher, the research institution or the research sponsor. Some industrial sponsors of academic research have contracts that enable them to suppress unfavorable research results
- Misappropriation - may include plagiarism, misuse of information in violation of confidentiality agreements related to review of grant applications or peer review of submitted manuscripts or exploitation of ideas gained from access to such confidential information

(Most of these definitions were taken from the website of the Office of Research Integrity of the US Department of Health & Human Services).

These problems of scientific misconduct are ones of overt personal dishonesty on the part of a few individual researchers seeking easy shortcuts to fame and fortune. It is intentional rather than inadvertent and does not include honest mistakes .

Honest Mistakes

But even competent researchers make honest mistakes. While the peer review process is traditionally believed to detect such mistakes and lead to correction, such inadvertent errors often remain undetected. The peer review process is far less effective at detecting errors in research and analysis and sometimes more political than some academics or journal editors may wish to acknowledge. Furthermore, many research projects are not likely to be repeated by others, which might find errors in the earlier work , because of the significant cost in time and financial resources. What is needed is a serious discussion among scientists about alternative methods for validation of research prior to submission for publication, and dissemination of results and recommendations.

Alternative Review and Validation Approaches

My colleagues at ECRI Institute in the US have found that periodic and tough critical review of research projects before, during and after they are undertaken may be more effective than the classical approach to peer review after the study is submitted to a journal. Our internal reviews include critical examination of proposed methodology, the collected data, laboratory notebooks and computer records and the analysis and conclusions based on that data. At several review milestones we add external reviewers to the team, intentionally nominating individuals likely to be antagonists. We insist that their objections and suggestions be taken seriously by the research project director and validated. This all precedes submission to a journal. We have institutionalized these processes and followed them for forty years.

Self Deception

One of the most significant cause of error is self-deception. This is not so much a matter of honesty and integrity but more a deficiency of character, a paucity of humility and surfeit of egotism. Perhaps it is a form of narcissism.

While some individuals may deny the existence or of an objective reality or the possibility of finding or understanding it, validating objective realities is the core function of and 'raison d'etre' for scientific research. The differences between what one believes and objective reality can be a function of ignorance, for which the antidote is education and experience, or it can be self deception.

Self deception is a process of denying or rationalizing away the relevance, significance, or importance of opposing evidence and argument. Typically, self-deception is used to maintain false beliefs in which one is emotionally, financially or otherwise invested and to which one is emotionally attached. Relinquishing such beliefs might call into question the individual's sense of self-worth and personal value. Self deception is the far more common threat to the quality and value of scientific research than is scientific misconduct.

Self deception is the persistence of incorrect belief about something because one's mind cannot:

- Encompass the possibility of being wrong
- Tolerate criticism
- Accept the possibility of alternative views that may have validity

- Accept the right of others to disagree without attributing ill-motive to them
- Appreciate the distinction between being in authority and being correct

Self deception in scientific research is an all too common natural consequence of the scientific method itself. The researcher starts with a theory and implements experiments intended to demonstrate the validity of that theory. There may already have been an emotional investment in generating the theory. The design of experiments themselves may be biased toward proving positive results, without which there is little to publish and little recognition. Some scientists have expressed the view, not entirely facetiously, that there should be a Journal of Negative Results – of failed theories and failed experiments. This would at least assure more publication credits even if theories were unfounded. There are certainly rich opportunities to undertake research in the phenomena of self delusion in scientific research.

Other Research Distortions

There is another category of actions which may not quite rise to the level of scientific misconduct but certainly must be considered inappropriate and questionable, such as:

- Photo-manipulation, without explanation which may mislead or be justified to clarify images
- Sloppy data collection and recording
- Careless data, laboratory notebook or computer record preservation that sometimes lead to 'convenient' losses
- 'Rounding errors' and 'extrapolation' that may tend to favor the researcher's wishful thinking
- Political correctness that distorts data analysis and conclusions

The Impact of Hierarchy

In the arenas of aviation safety, surgical risk management and military history who is senior and who is subordinate is well defined. Military history and in aviation safety and surgery there are many examples of disaster and human loss because a senior officer did not listen to a subordinate officer or non-commissioned officer, a command pilot did not heed a warning from his copilot, and a surgeon ignored a nurse or a resident or intern or even a medical student who was trying to warn of an imminent catastrophe in such events. In many such cases it is clear the superior was offended by the notion that he was about to make an error. It is the arrogance of position and power. Seniors usually believe their superior positions confer authority, and that, in and of itself means they know more, have more experience, and exercise better judgment. This may be true most of the time, but sometimes superiors are wrong and the junior person is correct. It only takes a moment to listen and consider the issue instead of ignoring it and scoffing at the junior persons temerity to question infallibility. It is no surprise, therefore, that the aviation accident rate is relatively high among surgeons flying private planes. Overconfidence is dangerous in many fields.

The same issue arises in academia and research. Research assistants struggling toward their doctoral degrees will be quite cautious about raising issues such as accuracy of measurements or recording of data in a project directed by the department chairman or their thesis supervisor. Medical research projects in several of the finest universities in the USA became institutional and personal scandals for department heads and senior researchers who scorned and then forced the resignation of subordinates who questioned the validity of methods or data or research records.

Self delusion feeds on overconfidence, the belief that seniority trumps concerns expressed by subordinates and a disinclination to listen to juniors, or, for that matter, to individuals you may regard as your challengers or even your enemies. If the devil himself knocks on your door and tells you your house is on fire, it would be wise to check your house for a fire rather than simply slam the door in his face and go back to sleep.

Conclusion

Scientific integrity is an expression of strong personal integrity applied to research. Checking and rechecking experimental work and inviting review by others will minimize inadvertent error. And humility and frequent and thoughtful introspection will diminish self-delusion. The safeguarding mantra is ‘Is it possible I may be wrong?’

7

Can Science Save the World?

Claudio Carlone

Let me begin with an apology. It is true that science is usually an input into economic activity that generates further prosperity, thereby increasing the quality of life.

However, science can also be an output that is pleasurable to indulge in, but which absorbs economic resources – rather than adding to them: like art, poetry, philosophy and so forth… which also contribute to the quality of life and the richness of culture. This is probably what we need now, more than ever.

Overpopulation may not be much of a problem today in Europe and North America, but it, and its consequences: hunger, disease and poverty, are ever more serious problems elsewhere in the world.

So, we are given a simple choice: spread as much culture as possible for sustainable development and population growth. Or we shall offer our descendents meaner, poorer, sadder and shorter lives.

Twentieth century life in the developed world is incomparably different from what it was like in the 19th century.

What led to these changes?

Surely, all the world's kings, presidents, and politicians played a role, but a minor one. So did all the world's architects, writers, and artists.

Most of the changes in our way of life resulted from advances in science, technology, and medicine. The history of civilization is closely linked to the history of science, much more closely than many scientifically illiterate historians may realize.

In a like manner, the 21st Century will be very different from the past century.

One thing, however, is clear: the relation between pure or fundamental science, on the one hand, and applied or practical science, on the other, has changed rapidly.

Medicine, despite its many triumphs, is not yet an exact science. Many new drugs, new devices and new procedures are devised every year. New therapies are added to the physician's tool-box. Nevertheless, it is still more an art than a science. But today, the human genome is to be widely mapped and many medical 'miracles' will become possible, soon, if scientist will learn how to deal with the immense amount of information contained in our genes.

Many dire diseases will become preventable or reversible.

Today, physicists, chemists, computer scientists, ethical philosophers, and biologists are working together to explore the most fundamental processes of life. Thanks to their very basic research, medicine is fast becoming a precise and quantitative science.

Many of the fundamental questions of physical science have been answered, at least in principle.

Those that still vex physicists have to do with things that are far too small or too far away to affect the everyday world. Finding out the rules was an essential first step, but there is a lot more to basic science than that.

Why?

Because, even knowing all the relevant rules, answering such a simple question as: 'why water is transparent and expands when it freezes' is devilishly difficult - let alone answering such tough questions as 'what the weather will be tomorrow?' or 'how a child learns to walk and talk?'.

There's more basic science to do today than ever before, and many unexpected wonders of nature are hidden in the complexity of things and not yet revealed to us. The so-called end of science is a mirage: science is truly the endless frontier.

An appropriate point to mention is the changing relationship between academia and industry.

As the distinction between basic and applied science blurs, it's downright silly to keep these enterprises entirely separate from one another.

University researchers should be encouraged to exploit their discoveries, just as industrial labs should pursue undirected basic research.

These traditions exist in the United States and in a few other countries, but not everywhere. We should anticipate and foster many even closer links between academia and industry in this century.

Ours is a technological society. Most of us can simply use such things as cars, computers, and cellular phones. But some of us must understand how they work, and others must address the problems that beset us, many of which were caused by the new technologies.

The functioning of modern society depends on our well-trained engineers and applied scientists. Who are they and who will teach them? Things have gotten much too complicated for on-the-job training.

Tomorrow's teachers and scientists are today's inquisitive children. Children often ask the same sorts of questions that basic scientists do:

'How did the world begin?, What makes stars shine?, How do rabbits make more rabbits?'

If only they could be encouraged to continue to ask these questions when they grow up… I'm suggesting what's called a bait and switch operation: get the kids interested in quarks and quasars so they learns some physics and maths, and maybe they will grow up to be scientists and invent a better battery or a new therapy.

Here is one more virtue of basic science. Science is one of a very few examples of successful international cooperation. This is not something new: science has rarely recognized national or cultural boundaries. For example, five men taught us our place in the universe: Copernicus (a Pole), Tycho Brahe (a Dane), Kepler (a German), Galileo (an Italian), and Newton (an Englishman).

Science continues as a multinational and multicultural enterprise, but today's scientists are no longer exclusively white, European, Christian men.

I shall conclude with one last argument for the importance of pure science, even when it is so pure that it offers no hope of immediate practical application.

No one said it better than Primo Levi: an applied chemist, a holocaust survivor, and a very moving author.

Please forgive me for offering an English translation of his Italian prose:

'What is the use of all this research? A world, in which only useful things are studied, would be sadder, poorer, and perhaps even more violent than the one fate has allotted us.

The future is uncertain even in the most prosperous countries, and the quality of life deteriorates; and yet I believe that what is being discovered about the infinitely large and the infinitely small is sufficient to absolve this end of the century and the millennium.

What a very few are acquiring in knowledge of the physical world will perhaps cause this period not to be judged as a pure return to barbarism'.

8

The Bibliotheca Alexandrina Supercourse: Expanding the Role of the Educator

Francois Sauer, Ron LaPorte, Susan Hanna Bennett

> 'If the afterlife had a library, it would indeed be heaven!'
>
> —Babs Mullins

When the Bibliotheca of Alexandria was burned, the unique content of its encoded explicit knowledge was destroyed. Two millennium later, the Bibliotheca of Alexandria Supercourse http://www.pitt.edu/~super1/ is transforming the public perception of a bibliotheca as a 'physical place with cuneiforms and books encoding explicit knowledge' to the concept of bibliotheca as a 'virtual space to relearn, evolve, and adapt.'

This transformation preceded by the 'Information Age' is being driven by a new quest for the assimilation of current knowledge and the proliferation of new knowledge in the 'Relationship Age'. In this new age where the speed of associations is pivotal to entrepreneurship and innovation, the role of the Educator is expanding to become a catalyst for the student's mind. We present some conclusions to support a generalized case of student-Educator relationships in the context of creativity and innovation in public health.

> 'Preparing humanity for worlds unknown, preparing our minds for thoughts unthinkable, and preparing our resolve for struggles unimaginable.'[1]
>
> —Futurist Thomas Frey

1. http://www.davinciinstitute.com/papers/the-future-of-colleges-universities-blueprint-for-a-revolution/

Introduction

The function and cultural role of libraries have changed significantly over the past several millenniums. Originally, libraries were the collection of knowledge in the form of objects (i.e. cuneiforms) with information in writing. They were 'owned' by royalties, and played a role in representing their particular cultural and religious identities. The first significant collection capturing knowledge outside of the immediate country's borders was the Ancient Bibliotheca of Alexandria.

The Ancient Bibliotheca of Alexandria, was one of the greatest libraries of the ancient world. Named after Alexander the Great, it flourished under the patronage of the Ptolemaic dynasty and functioned as a major center of scholarship from its construction in the third century B.C. and through 48 B.C. When the Bibliotheca of Alexandria was burned, the unique content of its encoded explicit knowledge was destroyed.

Today, the new Bibliotheca of Alexandria http://www.bibalex.org/, is one of the leading centers of physical and virtual scholarship in the modern world. The dimensions of the project are vast: the library has shelf space for eight million books, with the main reading room covering 70,000 m^2 on eleven cascading levels and is home to the Supercourse http://www.pitt.edu/~super1/index.htm comprised of a global health and prevention network of over 46,000 scientists in 174 countries who are sharing for free a digital library of 4,396 lectures in 31 languages. Two millennium later, the Bibliotheca of Alexandria Supercourse is transforming the concept of bibliotheca as a physical place with books encoding explicit knowledge to the concept of bibliotheca as a virtual space to 'relearn, evolve, and adapt' (Sauer, 2009). Soon the Bibliotheca of Alexandria will expand the Supercourse into the Science Supercourse covering in addition the domains of Agriculture, Information Technology and Environment.

Through observing the historical and sociological contexts for this transformation, we can draw some interpretations that extend beyond the digitization, preservation and archiving of collections. The omnipresent access of multiple media is inevitably transforming the educator-student relationship and the process of innovation within the context of that relationship.

This lens of observation may also have significant impact to the design of education policy and the educator-student relationship extending well beyond traditional confines of the academic life cycle.

We will begin with exploring the educator's role within a historical context and how the emphasis of certain expertise is changing as result of technology: we examine a viewpoint of the well understood Data-Information-Knowledge-Wisdom (DIKW) hierarchy, and place that in the context of the technology path of civilizations.

From Soil to Associations: Learning Elements of A Knowledge-Based Economy

> 'My art of midwifery is in general like theirs; the only difference is that my patients are men, not women, and my concern is not with the body but with the soul that is in travail of birth.'
>
> —Socrates (Cornford, 2003)

Socrates beautifully expresses his role as an educator in facilitating the birth of knowledge within men, exemplifying that throughout history, the 'educator' has been a philosopher and a student in the theory and practice of education. (Langenscheidt, 1998) While teaching (by a 'teacher') was a requirement for many in order to pass-on important instructions for survival, it used to be that education (provided by 'educators') was for the privileged few, whether due to sex or social status.

But the Industrial Age opened a space for mass training and education in global proportions, with nations today aware of the critical importance of facilitating their countries to compete in the new knowledge-based economy. A knowledge-based economy accelerated by the computer means that competition, now based on knowledge, can come from almost anywhere. While one effect is that students are in school longer, the other is that the knowledge-based worker is compelled to embrace a life-time of scholarship in order to compete.

What are the critical learning-elements of this knowledge-based economy? And how has technology itself shifted our approaches to learning? And how has it changed the educator-student relationship?

We begin by talking about these critical learning-elements so that we can adequately explain how technology has shifted our approaches to learning. In Figure 1, we present a model adopted from Clark and Bellinger, Castro

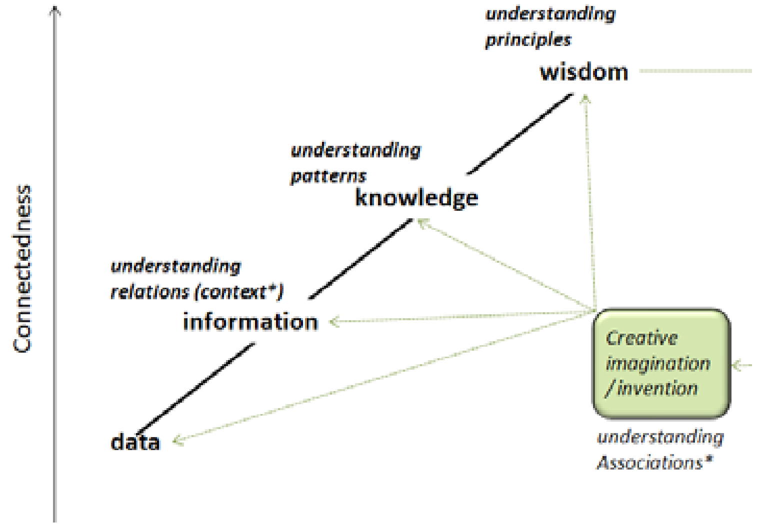

Figure 1. The Continuum of Understanding with Feedback

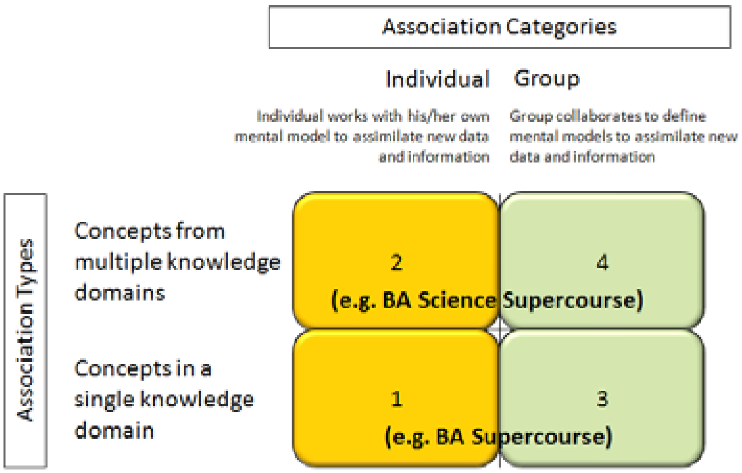

Figure 2. Categories and Types of Associative Capacity

and Mills. (Clark, 2004 & Belliger, Castro and Mills, 2004) This model helps to explain what we believe are critical learning elements. From a systems thinking standpoint, connectedness, a concept to describe the capacity for recognition of interrelatedness of organizations and structures, increases as the student moves from data assimilation to wisdom.

Now, what we want to add to Figure 1 is a 'feedback' mechanism for reflecting. This mechanism is activated by the gap between the student's expected or desired results and the observed results. The importance of this mechanism is that it provides a means for the student to identify how past experiences and belief systems have formed a mental model. This identification of a mental model in use in turn enables the student to engage creativity to modify his/her mental model therefore impacting the student's observations of new data, his/her stories about the past and expectations about the future. The understanding of this mechanism is critical to the validation and assimilation of current knowledge as well as the proliferation of new knowledge as today we now realize that 'we don't see with our eyes, but with our minds.' (Watt, 2009)[1]

Technology has had a tremendous impact on 'connectedness' – and to explain this further we redefine connectedness as an associative capacity. The capacity to 'associate' is defined here as the act of bringing ideas or events together in memory or imagination, or the act of relating resulting from interaction or dependence in an imaginative or creative way. (Langenscheidt, 1998)

There are two ***categories of association***, which we propose and are illustrated in (Figure 2) association on the level of the individual (quadrants 1 and 2 above), and association arising from the participation of two or more persons (quadrants 3 and 4 above). We propose there are two types of associations within each category: i) one type of association results from the creation of new concepts or relationships within a given knowledge domain (quadrants 1 and 3); ii) the other type of association results from breaking traditional silos and facilitating the creation of new concepts or relationships between multiple knowledge domains.

1. 'Even though our brains are being fed information at the same rate through our eyes, this is not how we see the world, because the brain is constantly making predictions and interpretations about what it sees. The problem is that these predictions are based largely on past experience: our brains make their best guess as to what they are seeing based on what we have experienced up to that point.' (Watt, 2009)

The capacity to 'associate' is a pivotal element to innovation and to the assimilation and proliferation of knowledge with technology having the effect of speeding these associations. The use of computers can help to break mental models by enabling or facilitating the cross-referencing between scientific fields (sometimes considered as silos) through the help of search mechanisms when information is digitized.

The Bibliotheca Alexandria (BA) Supercourse is an example of using technology to expand the capacity of both the individual and the group to 'associate'. The BA Supercourse can be used by the individual to explore concepts in a single knowledge domain: public health. And it is an example of using a network of people to collaborate towards expanding everyone's capacity to associate within the public health knowledge domain.

The Bibliotheca of Alexandria (BA) provides a highly-valuable offer now with the soon to be available Science Supercourse. The BA Science Supercourse increases associative capacity by bringing together concepts across multiple knowledge domains: agriculture, public health, information technology and the environment. Furthermore, it facilitates group collaboration helping to create new connections between people and subjects that may create a new concept, towards empowering the educator in his/her community.

The role of the teacher has been, up to this point in time, consistent in providing the student with the knowledge for researching, and guiding the student through the process of absorbing, doing, interacting and reflecting.[1] And we offer that this role has remained consistent regardless of the technology path – up to this point.

While civilizations change (see Figure 3) from hunting/agriculture bases, to the Industrial Age where energy is harvested, to the Information Age where data are harvested, or to the Relationship Age where technology now enables connections between concepts and people to be harvested, the environment of the 'Teacher' has evolved over time asking different questions:

1. How to hunt or cultivate?
2. How to manufacture? (Industrial Age)

1. Until now, knowledge was about interacting with the material world, vs. with concepts. At the conceptual level, it was for a very small elite of thinkers i.e. clergy or civil society, is now something that is everyone can access. The concepts of absorbing, doing, interacting and reflecting are borrowed from Clark (Clark, 2004).

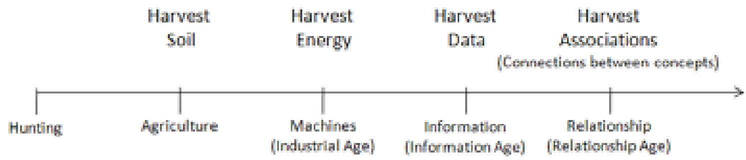

Figure 3. Technology Path

3. How to inform? (Information/Knowledge Age)
4. How to relate? (Relationship Age)

We have invented this new concept of the 'Relationship Age' to capture the existence of a social system that has been created as result of computer technology where geographic boundaries have become much fuzzier, there is a much higher economic and social interdependence globally, and our governments are grappling yet to understand the levers for managing equilibrium as a consequence of the death of distance between people: the information structures, because of the exploitation of computers closing geographical boundaries, are extremely challenging to define.

The role of teacher has evolved from teaching about how to make a living from specific domain knowledge, to being an educator, a student themselves in the theory and practice of education. And their role in content research, retrieval and information transfer is de-emphasized and has expanded to being a role model and guide of how to live in this Information and Relationship Age.

What this evolution, in some respects, has disguised, are the tools/frameworks employed by educators in the course of the Technology Path changes. Historically, after the invention of the 'press', books, and the evolution of the 'public library' equipped a workforce suitable for the industrial age, which helped a mass of workers assimilate knowledge and proliferate knowledge to a great extent. As of late we have seen roles models such as the Bibliotheca of Alexandria utilize the Internet to provide a new global ubiquity of digitized assets to facilitate the catalysis of the learning process.

In summary, the ubiquity of digitized assets means that the educator can leverage these so that he/she can de-emphasize his/her roles in the researching and absorbing component, and spend more time on emphasizing the doing, interacting and reflection components of understanding. From a nation's standpoint, the value-added role of the educator facilitates the possibility to 'leap-frog' in terms of technology paths and provides for a catalytic relationship with the student.

High Technology: Friend or Foe?

In shifting from the Industrial Age to the Information Age, high technology is perhaps culturally viewed with some distrust. It has been held responsible for enabling a significant shift of jobs across political and geographic borders, and in many instances rightly accused of removing the 'human' element from social interactions, such as the often inappropriate implementation of automated answering services with their never ending list of menus prior to getting a hold of a person.

We offer another consideration: high technology paradoxically also helps to manifest the relevance of the high touch of the human being. High technology speeds the interaction and contact between human beings by removing friction, costs and delays in our transactions. And it makes a one-to-one, one-to-many, many-to-one or many-to-many relationships development easier and faster to execute over physical distances. Facebook is an illustration of this new functionality. McAfee, now a principal research scientist at the MIT Center for Digital Business, calls tools such as wikis and blogs to Facebook and Twitter 'emergent social soft-ware platforms'.

What it means, is that mankind now has the potential to expand its relationships and touch, or use its free time and resources towards other endeavors including innovation.

In the Industrial Age and Information Age the role of the educator was, in part, driven by the need to cost-effectively educate the masses to perform to a minimum standard. They provided much needed access to research and methods for absorbing and doing. As class sizes grew, little space was left to promote interaction and reflection. Now the researching and absorbing and doing can be largely supported by the computer.

Today, in our digitalized knowledge world, for example the content of many of the lectures of the 'Nobel Prize' is instantly available worldwide through the Bibliotheca Alexandrina (BA) Supercourse. The soon available BA Science Supercourse will expand further this functionality. In this environment of 'just in time, all content available everywhere' in multiple media the value added of the educator more firmly rests in the domain of 'How to associate and relate?'

So, does the educator compete with the tools of the digitized world? Or is there a freedom produced that enables the educator to emphasize a more human, individualized approach to learning? And is this fundamentally a new role, or a different emphasis for this New Paradigm?

Changing Roles: The Educator as a Catalyst

By increasing the productivity of the educator, 'high technology' forums such as the BA Supercourse and Science Supercourse free the time for the educator to add 'high touch' value to her/his students. The 'high touch' tools in this Relationship Age, to borrow from Donnella Meadows, Dennis Meadows and Jorgen Randers, '…require the use of words that do not come easily from the mouths or word processors of scientists. They are considered too 'soft' to be taken seriously in the cynical public arena. They are: visioning, networking, truth-telling, learning, and loving.' (Meadows, Meadows and Randers, 1992) These forums empower the educator to stimulate the creative imagination of the students, evolving the role of the educator from:

a. Content provider; to
b. Catalyst for creativity and innovation.

In this new role of 'catalyst' the educator leads by example. The educator now has the responsibility to inspire the students to be all they can be, helping the student to manifest her/his potential to the fullest: educators continue to encourage students to reach beyond regurgitating facts, to dialogue about new ideas with educators potentially any time of day or night.

The educator as a catalyst also accelerates learning and discovery by opening up opportunistic relations with others in knowledge domains that can help the student. The educator by participating in the 'emergent social soft-ware platforms' helps students to interact with knowledge experts quoted in their lectures by providing them with the requisite connectivity. Therefore, the educator-student relationship becomes a bilateral doorway to knowledge and to local and global communities.

This function of 'catalyst' was for centuries embraced by only a select group of educators but today we propose that it will become the essence of the educator's value added. This New Paradigm of the educator as a catalyst, made possible now with the help of technology, represents a significant shift; this shift requires a major transformation in the thinking of many educators and a transformation to the environment of policies that support their activities.

The widening gap that results from technology impacts, and the more slowly changing social policies, is illustrated in the book 'The Laws of Disruption' by Larry Downes. Downes writes 'According to the Law of Disruption, technology changes exponentially, but social, economic and legal systems change incrementally… as human beings reorder their lives to adjust to new realities, the second order effects of innovation are both more dramatic and more systemic' (Downes, 2009). This is illustrated in (Figure 4).

As time progresses (x-axis) we see change (y-axis), as result of technology increasing exponentially (blue solid line), while change in the domains of social, economic and legal systems moving at a much slower pace (dotted sloped line). The graph illustrates the widening gap between technology and social, economic, and/or legal systems. The challenge in part, may be to not only transform the policy which constrains the operation of a New Paradigm of the educator as a catalyst, but to lead a cultural change in the expectations of the educator-student relationship.

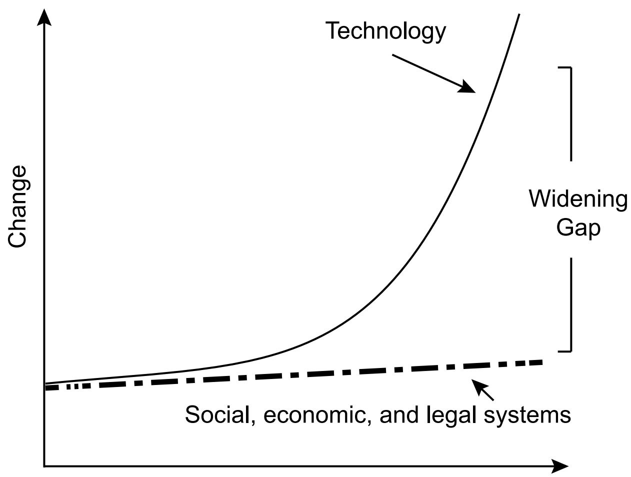

Figure 4. Relationship of Changes in Technology to Other Systems

Operating Principles for the New Paradigm

The operating principles of the New Paradigm, shared by the educator and student, are as follows:

1. Environment of Trust *vs.* External Control
2. Engaging the Creative Thinking Cycle
3. Systemic Thinking
4. Compassion
5. Courage and Resourcefulness

1. Environment of Trust vs. External Control

This New Paradigm of the educator as a catalyst, made possible now with the help of technology, enables a significant shift in the approach of designing curriculums that may be much more customized to the needs and interests of the individual student. Examples of this are undergraduate and graduate level self-study courses where students establish their learning objectives with the help of their educators who now take on a mentor role.

But this represents just one possibility of how high technology could enable a change in the education models. And these changes may require experimentation, which is necessary to validate new knowledge and wisdom to explore new creative possibilities.

This necessitates a profound cultural change. The Industrial Age created an environment where mistakes are threatening to production, and therefore intolerable. An environment of trust, in contrast, requires operating principles and ethics vs. the rules of the Industrial Age which were designed to enable external control. The new paradigm requires the maturity of the educator for guiding the student's development of commitment, sincerity, reliability and competency.

2. Engaging the Creative Thinking Cycle

Claude Bernard is credited for establishing the scientific methodology, characterized by hypothesis, experiment, observation of consequences, and a resolution to abandon existing mental models when facts don't fit the hypothesis.

The goal here is to engage our creative thinking to develop hypotheses when a gap between expected results and observed results is identified. Through association and our creative imagination we can now explore new creative options to perceive the current situation or elaborate on new mental models to understand the outcomes of previous experiments and test new hypotheses.

While the educator may bring new knowledge to the table on behalf of the student to help with creating new associations, the role of the educator actually shifts to instruction about how to find information and knowledge and bringing new tools to the student's attention so that they can engage collaboratively in the discovery of new associations to generate new data, information, knowledge and wisdom.

3. Systemic Thinking

Jay Forrester, professor emeritus of the Sloan School of Management at MIT, is often credited with the development of systems thinking. Systemic thinking enables us to observe over time the impact of associating different concepts described in terms of levels and rates. It helps the observer to explicitly define the boundaries of the system in which he or she operates.

We apply systemic thinking to the management of one's own thinking. System thinking offers to the individual or group the opportunity to specify and self-manage our presuppositions and the system boundaries of our thinking. It involves experimenting and observing the limits or barriers we create in our minds vs. what is the observed behavior of what we choose to model. It involves being an observer of 'external control' and where it lives in one's one mind as cultural or traditional, the historical reasons for its existence and questioning with openness the need for its continued existence. It involves being an observer of where new policies may need to be implemented or where there will be difficulty and assessing their systemic long term and global consequences to ourselves and/or others including our environment.

In the New Paradigm, the educator plays the important role of mentor and guide in developing the student's capacity for reflective systemic thinking and for moving the student from 'I' to 'we' and recognizing the connectedness of our planet. This calls expansion of the educator's interdisciplinary knowledge and leadership training.

4. Compassion

Without compassion for self and others, it is difficult to be creative because we are then the prisoners of our conditioned judgments, comparisons and evaluations. Our basic biological mechanisms, operating in 'flight or fight' in stressful situations, collapse the space within which creativity can operate and thereby tend towards stopping the reflective process. Compassion helps us deal with the stress associated with our perceived failures that we can now label as feedbacks. Compassion helps us to let go for the need to be right therefore freeing our mind when feedback invites us to engage our creative imagination to explore new possibilities to evolve our current state.

5. Courage and Resourcefulness

Courage enables us to move forward, with an empowered self-esteem and test the results of new associations, while resourcefulness both within ourselves and with our communities enables us to creatively address the inevitable breakdowns of experimentation.

> 'The mind, as a parachute, only works when open.'
>
> —Source Unknown

The challenge, in this knowledge world, is that our mind may be in different states of receptivity and creativity. It is the role of the educator to create an environment of courage and resourcefulness that facilitates the activation of the creative imagination of the student. Today the educator has a great responsibility in modeling the virtues of courage, resourcefulness and compassion for students to better contribute to the development of our worldwide community. Each nugget of knowledge may be a step stone or a fence – it can imprison us or propel our creativity.

Mapping the Educator's Value-Added to Virtual Knowledge Forums

The BA Supercourse is an example of how multi-media virtual knowledge forums and leadership can expand the value – added of the educator towards facilitating the development of the student's creativity and innovation.

Multi-media virtual knowledge forums have the potential, especially with the aid of semantic based search engines, to free the educator's time from undertaking course material preparation to performing roles as mentor and leader. High technology communication forums also hold a promise to make it easier for educators to build and maintain a connection with students half a world away and throughout their careers. The educator can stay on as an 'anchor' to the students helping them to be more centered due to this historical connection.

Below is a table that maps the relationship of the BA Supercourse to an educator's value added, as a possible general model of operating in this proposed New Paradigm of catalyst.

Bibliotheca Alexandrina (BA) Supercourse value added	Educator's value added as a catalyst
Leverage quality and availability of content for better lectures.	Be genuinely interested in the success of the student. Use the time and technology to undertake leadership training, receive and give immediate feedback, and make connections outside of the classroom.
Reducing preparation time increases productivity and frees educators to spend quality time 'high touch' for relating with students.	Able to emotionally connect with the student. Serve as a catalyst to build student-student relationships, student-community relationships and global connections.
Stress the need to customize the lectures to optimize the assimilation of knowledge leveraging creativity and innovation in a way that is respectful of the community culture.	Meet the student where he/she is in his/her intellectual and emotional development, honoring the needs of his/her student as well as the needs of the community.
Provide feedback to monitor the usefulness of content.	Nurture an environment of trust understanding and compassion.
Facilitate a 'Just in Time' multi-disciplinary and multi-cultural approach to key topics as earthquake or flu.	Create new associations between ideas and between peoples in different knowledge domains. Move towards global knowledge sharing and global relationship sharing.
Benefit from the BA Supercourse participants who provide feedback to, over time, improve the quality of the content.	Model an open mind and therefore choose to be vulnerable and to acknowledge his/her limitations showing that he/she is capable to relearn, evolve and adapt. (Sauer, 2009)
Empower the educator as a role model who chooses how to best leverage the content provided by the BA Supercourse as a reference	Provide a blueprint for problem solving that enables the student to, with courage, access his/her own resourcefulness, to think systemically and creatively fostering an environment of respect for the opinions of others.
Embrace presentations with different perspectives on the same subject	Tolerate ambiguity to leverage creativity and innovation.
The educator is central to the presentation of his/her lecture. The BA Supercourse fades in the background.	Be ready to let go.

The BA Supercourse as a space to 'relearn, evolve, and adapt' is the virtual space that enables interaction between real people. We are all interconnected including, for example a student in Kansas[1] with a Nobel Prize winner presenting at BioVisionAlexandria 2010. In this cyberspace, the knowledge of humanity is becoming malleable and fluid. Now through associations new knowledge will be created from the generative process in the mind of a creative person exposed to new nuggets of knowledge as well as in the generative dialogue, enabled by the BA Supercourse, between creative people.

This high technology world and its tools hold a promise to remove certain traditional Industrial Age practices or reduce time burdens such as lecture preparation, allowing educators the space to tailor the education to individual students possible through the use of new tools including 'emergent social soft-ware platforms'. Today, graduate mentorship produces much more highly trained and skilled students than classroom education. Forums like BA Supercourse and other tools offered by high technology may enable graduate style mentorship at more elementary levels of education. The vision presented is that of the educator as a mentor, a leader, and a facilitator of innovation that is highly ethical and relevant to the community.

Conclusions

Computers continue to get faster, cheaper, and smaller. And the application of Moore's Law and Metcalf's Law have significant on-going and yet-to-be-seen second-order effects on our social and economic structures. The capacity now at our fingertips has created an unprecedented explosion of scientific discovery. But the gap between scientific development and our ability as a community to socially assimilate these discoveries is also growing exponentially.

New social constructs are playing 'catch-up' with technology and scientific discovery. And this forms the platform for the argument that the role of educator is a strong candidate, perhaps even stronger and more influential

1. Reference U.S. President Obama's speech in Cairo regarding connectivity between a student in Kansas and a student in Cairo. http://www.huffingtonpost.com/2009/06/04/obama-speech-in-cairo-vid_n_211215.html 'On education, we will expand exchange programs, and increase scholarships, like the one that brought my father to America, while encouraging more Americans to study in Muslim communities. And we will match promising Muslim students with internships in America; invest in on-line learning for teachers and children around the world; and create a new online network, so a teenager in Kansas can communicate instantly with a teenager in Cairo.'

than governments, to help our communities to responsibly exploit the opportunities presented by sciences and technology.

The Bibliotheca of Alexandria, within this multi-disciplinary scientific environment, is implementing technology to offer to the community new ways to access available knowledge. And the fact that the Bibliotheca of Alexandria made the decision to become totally virtual and completely based on technology was a courageous decision because it puts it as the first bibliotheca organization not depending of a collection of books.

As critically, it expands the capacity within categories of association facilitating the breakdown of traditional silos because of the ease of cross-referencing between scientific fields compared with a traditional library. Soon we can anticipate a merged digital search engine that will be able to extract meaning and therefore facilitate conceptual associations between different domains.

But despite the useful tools and resources now made available, the role of educator as a catalyst of associations needs political support. In this New Paradigm where assimilation and proliferation of new knowledge are pivotal to nurturing grass-roots creativity and invention towards innovation, the educator needs supportive policies to set expectations about the shift in emphasis of their role from being data and information conduits, to working with students as individuals helping to customize learning, assessments of progress, and provide more philosophical foundations that enable the student to set appropriate boundaries and become observers of the interconnectedness, of their learning and their communities.

This new role requires leadership education, a foundation in ethics and philosophy, community relations education and facilitation skills that extend cross-cultural boundaries to equip the educator for their role in global knowledge and relationship sharing. A life-time of scholarship in order to continue to be effective is required for both the educator and the student, with the educator being a role-model in the ethical application of the findings of Science.

> 'Science sans conscience n'est que ruine de l'âme'
>
> —François Rabelais.

One domain where the issues of interconnectedness, learning, and innovation must be managed more expeditiously is public health. The gap between technological innovation and social elements (i.e. culture, politics, law) is becoming untenable in terms of the effectiveness of politics. And the question then becomes is there a new operating model that is made possible with the help of educators?

Biologically, we are designed to 'couple' to each other in language when there are recurrent interactions (Maturana and Varela, 1987). This is known as structural coupling. Fernando Flores, a businessman, educator and philosopher purports that we can use language deliberately to 'consciously shape' our future (Fisher, 2009). Educators, because of their daily work with students, have an opportunity to enable structural coupling rivaled by perhaps only the television. Might this offer the possibility of instilling a set of operating principles within students that enable our next generation to move with a higher velocity while protecting the concerns of the community? And if so, how do these operating principles get decided? And how do you manage the local and/or global development of these operating principles?

'The student of tomorrow will need to be prepared for a higher calling. This higher calling will be to preempt crisis before they occur, anticipate disasters before they happen, and solve some of mankind's greatest problems, starting with the problem of our own ignorance' (Frey, 2009).

It is perhaps ironic, that high technology presents this unique opportunity, and just as the Bibliotheca of Alexandria was unique and exclusive in its origin, it is now, again, the first in being unique and inclusive in its ability to open an unprecedented capacity for educators to make this shift from content provider to catalyst for the student's mind. We believe that the offered operating principles for the educator to be a catalyst provides some unique perspectives for a more powerful integration of education, scientific discovery, business and innovation.

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9

'Twelve Points of Light' for Creating a Technology Transfer Program

Joseph D. Fondacaro

Introduction

In the past thirty years, the number of technology transfer offices in universities and other academic research institutes and medical centers has increased substantially in all parts of the world. While the United States has led this increase, mainly following the enactment of the Bayh-Dole Act of 1980, many academic research centers in other countries in Europe, Asia, Australia and Africa have pursued this enterprise and a means of creating opportunities to provide for the public good and, in the process, hopefully secure a monetary reward back to the center to support more research and teaching activities.

There are many mechanisms, processes, procedures and policies for running a technology transfer office in the academic setting. While these may vary from country to country, there are a few important principles that are common to many, if not most, programs and that have proven to assist the technology manager in maintaining a successful technology transfer program in the academic setting.

This discussion to follow outlines the 'Twelve Points of Light' as guiding principles for creating a successful technology transfer program in academic research centers.

Point of Light (1) Technology Transfer for Public Benefit

There are several important reasons why an academic research center would choose to do technology transfer. However, it must be kept in mind that research yields new knowledge and often times this new knowledge, when used in a more pragmatic sense, can benefit many thousands of people, not just the investigator who discovers the knowledge. Therefore, the primary reason why academic centers do technology transfer is for public benefit. This is so clearly pointed out in the 'Better World Report', published by the Association of University Technology Managers (AUTM). New knowledge discovered by a scientific investigator benefits the investigator through publication of the results and the career recognition it brings to the individual. However, if the new discovery is then translated into a product that can, for example, treat an incurable disease or in some way improves the quality of life for a patient, the public benefit of technology transfer is immeasurable.

There are other reasons for doing technology transfer. These activities provide for faculty satisfaction in seeing his/her discoveries benefit the public or help the investigator establish new lines of collaboration with scientists in for-profit companies. Technology transfer also provides many opportunities to forge relationships with industry, both for the scientist and the technology transfer professional. Often the best mode of commercializing a technology is via creation of an academic start up company. In these cases the technology transfer program is contributing to the growth of a regional economy by providing jobs and an avenue for local investments. Finally, a technology transfer program does, on occasion bring significant revenue into the university. However, most of the time a single program in a university will earn enough revenue to 'break even' or finish a year on the positive side of the financial ledger. All things considered, in the end the public benefit that is created by transferring discoveries from academic laboratories to industry for product development and ultimately public use is by far the most rewarding return to an academic research university with a technology transfer program.

Point of Light (2) Build Trusting Relationships

There are many procedures, processes and programs that one has to follow as a technology transfer associate. Furthermore, there are a multitude of people one has to interact with to make a successful program. Contained in all of this is the ability to build and maintain relationships—the most important of all the procedures and processes one performs as a technology transfer professional. As such, you are dealing with faculty/inventors, administrators, attorneys, licensees, other colleagues in technology transfer and stakeholders in your program. In addition, you will do marketing, valuations and patenting which will require interaction with other specialized individuals. Thus, building relationships that are meaningful, trusting and enduring will ensure a successful technology transfer program in your university or research center for many years in the future.

Point of Light (3) Manage Expectations

Technology transfer means many different things to many different people. Thus the expectations of your program will be as varied as the individuals with whom you interact daily, namely researchers, administrators, investors and colleagues. Critical to many universities is the 'return on investment' from licensing royalties. Administrators and inventors are looking for the 'big money payoff' in exchange for the time, effort and financial support given to your program. Likewise, community leaders are anticipating that your program will provide small business opportunities and jobs for the region. Lastly, companies are anticipating that your research center will provide them with near market-ready technology. It is the experience of those in this field that many, if not most, of these expectations are part of having an academic technology transfer program. Thus, it becomes important to the success of your program that you manage expectations of these stakeholders. It is important also to remind them often that the reason for doing technology transfer in academic research is for public benefit (Point of Light 1 above). Don't set expectations too high initially; the fall may be painful in more ways than one!

Point of Light (4) Expand, Not Change, the Culture

The academic research environment has a long standing and well defined culture. Once in their 'comfort zone' investigators, teaching faculty, researchers and administrators don't accept change in their cultural sphere very well. They have over time invested much of their lives and resources in building their reputation and their laboratory to a successful enterprise and they would not like to see these things change. Thus, for a technology transfer professional to come in, establish an office and suddenly announce that 'we are going to change the culture to bring about more awareness of commercialization of technology from academic research' will be viewed as a potentially serious threat to the well-being of many. Instead, the endpoint of building a successful technology transfer program comes with working with staff to 'expand' the culture to include technology transfer. Your job does not require a change in the academic culture. However, once a working relationship grows to the level of mutual trust, a very successful symbiotic relationship can exist between the academic culture and the business-oriented culture of technology transfer in most university research centers. The inference here is that this approach goes hand-in-hand with point #2, building relationships.

Point of Light (5) Know Something about Intellectual Property Law

To be a successful technology transfer professional and to have a successful program in technology transfer, one much be familiar with, for example, the definitions of prior art, invention, non-obviousness, best mode, reduction to practice, enabling and other terms and terminology that are somewhat unique to the field of patent and copyright law. In reality, you will be dealing with these issues on a daily basis regardless of the size of your program. So, it is an important matter to learn what you can about intellectual property law in your country and how these principles apply to the global intellectual property environment.

Point of Light (6) Inventorship *vs.* Authorship

To go along with the previous point, often times in the academic setting, investigators will confuse the definitions of authorship and inventorship as they apply to scientific publications *vs.* patents, respectively. Inventorship is defined by patent law and as such, any misrepresentation of inventorship on a patent may indeed threaten the validity of a patent if challenged by a third party. Therefore, being familiar enough with these definitions so as to be able to explain them clearly to your inventors, again utilizing the relationship you've built with them, one can avoid many serious and often contentious discussions and incidences. Seek the advice, support and possibly the services of a competent intellectual property attorney before entering into these discussions with inventors.

Point of Light (7) Know the Value of Early Stage Technology

Universities and other academic research centers do basic research as part of their mission; to create and disseminate new knowledge. However, academic research centers, for the most part, do not do product development. Therefore, by definition, the research innovations discovered in academic centers are early stage technologies and most often are far from being products. A given technology will require proof of concept or proof of principle testing, prototype development and/or commercial utility before it is truly considered a low risk opportunity for a potential licensee. Therefore, within the technology transfer program of a university, one much consider their technologies early stage and, for the most part, not of great value. The value exists in what resources the university and the investigator has invested to get to the identification of the innovation. Therefore, a successful licensing program within an academic research center must approach licensing of their technology with this in mind and not 'overprice' their technologies. The proof of the real value will come as a product evolves from the technology after it is licensed to a company that can truly do the development work to get it to a marketable product.

Point of Light (8) Know Why Companies License Technology

There may be various reasons a company wants to license a certain technology from an academic research center. However, over the years, it has become apparent that there are five main reasons why companies seek and license technology from universities. A company may need a technology to answer a question that has arisen within their own produce development process. Likewise, a company may have encountered a problem with the development of a technology of their own and they seek to license an available technology to assist them in solving that problem. Also, a company may see a technology that would in some way enhance their own product and thus they seek to license that technology. A gap may be present within a certain product line or market need and the company sees a certain technology from an academic center as something that can assist them in filling that gap. Finally, a company may be looking to begin a new franchise and needs technologies to fill the pipeline of the new enterprise. So companies will license technology to 'jump start' the new franchise. Keeping these reasons in mind will help a technology transfer office in the marketing of their discovery and identifying the right licensee for their technologies.

Point of Light (9) Learn How to and Make Time for Marketing Technology

It has long been known that targeting the right company for licensing your technology is the most direct way to achieve a successful technology transfer program in the academic research setting. So market research is a key component of this process. Investing time in good market research increased the return in value of a license and knowing how to position your technology within a market is essential.

To successfully market your technology, it is critical to know your technology. Once the potential licensee companies are identified and before contacting them, it is important to know the 'Value Proposition' that is being offered by your technology. Be sure to identify the feature/benefit relationship and remembering features attract attention, benefits sell the technology. Besides the value proposition, determine whether your technology is a 'me too' or 'look alike' technology to others on the market. Perhaps your technology is an incremental improvement when viewed against other technologies. Your technology may be a 'platform technology' out of which many different products could potentially be developed. And finally, your technology could be a 'disruptive technology', one that will displace the competitors in the market.

When researching potential companies to contact about licensing your technology, find out first the company's strengths and needs and learn who the appropriate contact is within the company. Then it is time to 'put down the mouse and pick up the phone' so that you are talking and building a relationship with the person with whom you may be negotiating a license in the future.

Finally, good technology marketing practices are often given less of a priority than other activities within a technology transfer office. It is highly recommended that good marketing and market research practices not only be established but are also given a high priority.

Point of Light (10) Understand the importance of the Invention Disclosure

An invention disclosure is generally the document used by technology transfer offices when they are first informed that their investigators have a novel or innovative technology, one that has the potential to be a license candidate leading to a product. The invention disclosure is considered by many to be the 'Cornerstone' of a technology transfer program. Without invention disclosures, one has nothing to eventually license. Therefore, it stand to reason that critical importance be given to these documents.

Create a simple but thorough questionnaire-type document that will provide you with information you need to make a decision as to whether to pursue a patent application and a license or whether the technology needs further investigation by the inventor before a patent is filed. Once you have the completed document, do a thorough job of assessing and 'triaging' the document and information within as the information is what will guide your decision to move forward with patenting and licensing the technology.

Finally, every disclosure should receive the same level of scrutiny as you do not know at the outset which discovery will prove to be the 'crown jewel' of your portfolio.

Point of Light (11) Practice Good Office Management

A technology transfer office in an academic research center sits at the interface of the academic culture and the business world. It also sits at the interface of being a service organization to faculty and a revenue center for the university. Thus, it takes uniquely qualified individuals to work in this environment. Well trained technology transfer professionals are a key to making the office successful. Therefore, screen candidates thoroughly and hire the right associates, those who understand and can work within the academic culture. It is important that all associates in an office be responsive to faculty researchers and administration as they provide, respectively, the disclosures you need and the resources you require to be successful. It is important also to get involved in university programs especially faculty research seminars. These and other good office practices will go a long way to making your technology transfer program a success.

Point of Light (12) Get Involved in Professional Societies

Most, if not all, of what is discussed above are proven principles of successful technology transfer. Many are standard procedures that have been used for many years and are known by those who practice this art. Many of these professionals are members of societies and meet regularly to discuss these principles, the standards of practice and their experiences in dealing with change or adversity. These individuals make for an invaluable resource and should be part of your professional network. Likewise, these professional societies offer professional development courses that deal specifically with the good practices in technology transfer. It is highly recommended that new and even experienced technology transfer professionals join these societies.

The major society is the Association of University Technology Managers (AUTM), based in the United States. They hold a series of meetings and professional development classes every year. Likewise, certain individuals within AUTM are licensed to provide professional development training in foreign countries. AUTM membership is made up primarily of academic technology transfer professionals. AUTM can be accessed through their website, www.autm.net.

Another such organization is the Licensing Executive Society (LES). LES likewise holds several meetings and professional development courses each year. The membership of LES is primarily from the private sector businesses that are active in technology licensing. They can be accessed through their website, www.les.org.

Conclusion

Technology transfer in the academic research setting is a unique, exciting and rewarding endeavor. The author has attempted to define a critical path for individuals, administrators, universities and other academic research centers who are contemplating the establishment of a technology transfer office. It is hope that these 'Twelve Points of Light' provide the reader with guidance, knowledge and encouragement to pursue this most worthwhile enterprise.

Acknowledgement:

The author wishes to thank Dr. Morris Berrie and BioVisionAlexandria 2010 for the kind invitation to speak at this important conference.

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3

SCIENCE FOR FOOD, AGRICULTURE AND SUSTAINABILITY

10

Biodiversity and Biotechnology: Myths and Reality

Klaus Ammann

Myths About ‘Monocultures’

Species and genetic diversity within any agricultural field (organic or conventional) will inevitably be more limited than in a natural or semi-natural ecosystem. Surprisingly enough, many of the crops growing in farming systems all over the world have traits of ancestral parents which lived originally in natural monocultures (or better ‘monodominant fields’. (Wood & Lenne, 2001). This is, after all, most probably the reason why our ancestral farmers chose those major crops. Indeed, (Fedoroff & Cohen, 1999) reporting (Janzen, 1998, 1999) use the term ‘natural monocultures’ in analogy with crops. Such monodominant stands may be extensive. As one example out of many, Harlan recorded that for the blue grama grass (*Bouteloua gracilis*): ‘stands are often continuous and cover many thousands of square kilometers of the high plains of central USA.’ It is of utmost importance for the sustainability of agriculture to determine how these extensive, monodominant and natural grassland communities persist and when and if we might expect their collapse.

The wild variety of *Sorghum* (*S. verticilliflorum*) is the widest distributed feral complex of the genus, with a broad climatic plasticity, extending almost continuously east of 20° east longitude from the South African coast to 10° north latitude. It overlaps along its northern and northwestern borders with *S. aethiopicum* and *S. arundinaceum*, again hybridizing extensively. It grows over large areas of tall grass savannah in the Sudan Typically enough, (Ayana et al., 2000) found a remarkably narrow genetic basis for the variety *verticilliflorum* in their analysis. Wild rice is another perfect example of monodominant populations: (Harlan, 1989).

Agricultural Eco-Systems Are Dynamic

Agricultural ecosystems can be dynamic, in terms of species diversity, over time due to management practices. This is often not understood by ecologists who involve themselves in biosafety issues related to transgenics. They still think in ecosystem categories close (or seemingly close) to nature. Biodiversity in agricultural settings can be considered to be important at a country level in areas where the proportion of land allocated to agriculture is high: Ammann in (Wolfenbarger et al., 2004). This is the case in continental Europe for example, where 45% of the land is dedicated to arable and permanent crops or permanent pasture. In the UK, this figure is even higher, at 70%. Consequently, biodiversity has been heavily influenced by man for centuries, and changes in agrobiological management will influence biodiversity in such countries overall. Innovative thinking about how to enhance biodiversity in general, coupled with bold action, is critical in dealing with the loss of biodiversity

Consequently, biodiversity has been heavily influenced by humans for centuries, and changes in agrobiological management will influence biodiversity in such countries overall. Innovative thinking about how to enhance biodiversity in general coupled with bold action is critical in dealing with the loss of biodiversity. High potential to enhance biodiversity considerably can be seen on the level of regional landscapes, as is proposed by (Dollaker, 2006). It is therefore not surprising, that a recent study demonstrated, that on a landscape level, conventional farming produces at least or even more biodiversity than organic farming (Gabriel et al., 2010).

Myths about Centers of (Crop)-Biodiversity

Biodiversity should still act as biological insurance for ecosystem processes, except when mean trophic interaction strength increases strongly with diversity (Thebault & Loreau, 2005). The conclusion, which needs to be tested against field studies, is that in tropical environments with a naturally high biodiversity the interactions between potentially invasive hybrids of transgenic crops and their wild relatives should be buffered through the complexity of the surrounding ecosystems. This view is also confirmed by the results of Davis (Davis, 2003). Taken together, theory and data suggest that compared to intertrophic interaction and habitat loss, competition from introduced species is not likely to be a common cause of extinctions in long-term resident species at global, meta-community and even most community levels.

There is a widespread view that centers of crop origin should not be touched by modern breeding because these biodiversity treasures are so fragile that these centers should stay free of modern breeding. This is an erroneous opinion, based on the fact that regions of high biodiversity are particularly susceptible to invasive processes, which is wrong. On the contrary, there are studies showing that a high biodiversity means more stability against invasive species, as well as against genetic introgression (Morris et al., 1994; Tilman et al., 2005; Whitham et al., 1999). There is more evidence, that biological invasions, and thus also transgenic hybrids of wild relatives of GMOs with a potentially higher fitness, depend on a multitude of factors, some now with recent research stepwise identified: (Von Holle & Simberloff, 2005).

Biotechnology Contributes to Biodiversity

The main theme of this paper is to demonstrate that transgenic crops such as *Bt* events and glyphosate tolerant events contribute in a clearly positive way to the biodiversity of non-target insects and soil microbiology. There are literally hundreds of scientific publications supporting this statement, a small selection is presented here.

A case study for high-altitude rice in Nepal by (Joshi & Witcombe, 2003) has demonstrated that participatory rice breeding can also result in a positive impact on rice landrace diversity. With the exception of two villages, the varietal richness among adopting farmers was either static or increased, and there was an overall increase in allelic diversity. However, this positive picture could change with an inconsiderate introduction of modern traits.

Biodiversity is not hampered by the cultivation of GM crops per se (Ammann, 2005), on the contrary, *Bt* crops for instance need less pesticide sprays and consequently, non-target insect populations are considerably better off in *Bt* maize and also in *Bt* cotton as shown below. Herbicide tolerant crops, which allow for almost 100% no-tillage management, enable better soil fertility: Major meta studies have proven that biotechnology crops can help to enhance biodiversity as a whole: for details and discussions I recommend the two case studies of herbicide tolerant and *Bt* crops that follow:

The Case of Herbicide Tolerant crops

The value of reducing tillage has long been recognized as beneficial for soil systems, but the level of weed control a farmer required was viewed as a deterrent for adopting conservation tillage. Once effective herbicides were introduced in the latter half of the 20th century, farmers were able to reduce their dependence on weed-killing tillage. The development of crop varieties tolerant to herbicides has provided new tools and practices for controlling weeds and has accelerated the adoption of conservation tillage practices and accelerated the adoption of 'no-till' practices (Bonny, 2008; Fawcett & Towery, 2002). Herbicide tolerant cotton has been adopted rapidly since its introduction (Fawcett et al., 1994). In the US, 80% of growers are making fewer tillage passes and 75% are leaving more crop residue (Cotton Council, 2003). In a farmer survey, seventy-one percent of the growers responded that herbicide tolerant cotton had the greatest impact on soil fertility related to the adoption of reduced tillage or no-till practices (Cotton Council, 2003). Today, the scientific literature on 'no-tillage' and 'conservation tillage' has grown to more than 6,500 references. Several important reviews have been published in recent months, they all tell a positive story regarding the overall impact of herbicide tolerant crops and the impact on the agricultural environment: (Christoffoleti et al., 2008; Locke et al., 2008; Norsworthy, 2008; Wang et al., 2008) and the more recent studies: (Green & Owen, 2010; Powell et al., 2009; Sheridan, 2010).

The Impact of *Bt* Maize on Non-Target Organisms

(Candolfi et al., 2004) stands as a study which, like many others, gives a positive message about *Bt* maize and non-target insects. The same is valid for cotton fields (Cattaneo et al., 2006): Five meta studies have been published recently with more or less stringent selection of data published in scientific journals, and none of those meta analyses show any sign of regulatory problems. (Chen et al., 2008; Duan et al., 2008; Marvier et al., 2007; Wolfenbarger et al., 2008)

(Wolfenbarger et al., 2008) is singled out here, since it is the best meta-analysis existing so far, the selection criteria are clearly defined on all levels and based on a carefully filtered dataset, actually a subset of the database published by (Marvier et al., 2007) on the internet under www.sciencemag.org/cgi/content/full/316/5830/1475/DC1.

In total, the database used contained 2981 observations from 131 experiments reported in 47 published field studies on cotton, maize and potato. Maize has been studied in the following two comparison categories (including also data on potato and cotton).

- The first set of studies contrasted *Bt* with non-*Bt* plots, neither of which received any additional insecticide treatments. This comparison addresses the hypothesis that the toxins in the *Bt* plant directly or indirectly affect arthropod abundance. It also can be viewed as a comparison between the *Bt* crop and its associated unsprayed refuge (Gould, 2000).
- The second set of studies contrasted unsprayed *Bt* fields with non-*Bt* plots that received insecticides. This comparison tests the hypothesis that arthropod abundance is influenced by the method used to control the pest(s) targeted by the *Bt* crop. (The third set of studies contrasted fields of *Bt* crops and non-*Bt* crops both treated with insecticides, a category which did not occur in the studies of maize included here).

As a whole, the study of Wolfenbarger et al. did not reveal any negative effects, confirming for a large amount of data and publications the environmental benefits of the *Bt* maize tested.

More details on modern agriculture and biodiversity are given in the following report:

- http://www.botanischergarten.ch/Biotech-Biodiv/Report-Biodiv-Biotech12e.pdf see also the follow up blog in ASK-FORCE:
- http://www.ask-force.org/web/AF-11-Biodiversity/AF-11-Biodiversity-Biotechnology-20100715-opensource.pdf

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11

Agriculture and Biodiversity in a Hot and Crowded World

Nina V. Fedoroff

Summary

Science and technology have supported extraordinary gains in global agricultural productivity over the past two centuries, allowing mankind to expand from a population of 1 to almost 7 billion. However, this vast agricultural expansion has resulted in profound losses in biodiversity. Looking to the future, climate change and continued human population growth demand a further substantial increase in the world's agricultural productivity. Reducing the water demands and ecological impact of agriculture and developing crops suitable for a hotter world while increasing the overall food supply will require unparalleled developments and improvements in agricultural and food sciences and technologies.

Concerns about food security are as old as mankind. Thomas Malthus' famous 1798 'Essay on Population' crystallized the concern for modern times, arguing that humanity was doomed to poverty and famine because the human population grew exponentially, while mankind's ability to produce food could only increase at a linear rate (Malthus, 1798). Curiously, it was at about the same point in history that science entered agriculture with Priestley's discovery that plants emit oxygen (Priestley, 1774), followed by landmark discoveries about how plants convert simple gases, minerals and water into foodstuffs. Over the subsequent two centuries, scientific and technological advances have driven extraordinary increases in agricultural productivity.

Particularly important was the development of a method early in the 20th century for converting atmospheric nitrogen to forms that plants can use (Russel and Williams, 1977). Nitrogenous fertilizers are now synthesized in huge plants around the world.

Another important development was the mechanization of farming, which has spread throughout the world, though much more so in developed than in developing countries. Today's most advanced precision agriculture is indeed technologically sophisticated, using GPS-guided tractors, materials such as plastics that retain soil moisture and control weeds, and complex integrated pest management strategies.

Well before science and technology entered the agricultural arena, humans had made some considerable progress in the genetic modification of plants to make them into food crops (Fedoroff, 2004). Corn (also known as maize) came from a grassy relative called teosinte. Corn and teosinte are so different that they were originally assigned to different species, yet they proved so closely related that they can be crossed to produce fertile off-spring. Over thousands of years, people have converted this grass to one of humankind's most productive crop plants. But the truly dramatic expansion of the ear took place largely during the 20th century, when it was discovered that seeds from a cross between two highly inbred, rather small and weak plants gave much more vigorous plants with much larger ears in the first generation. This is called hybrid vigor and is the basis of our current extraordinarily productive hybrid corn varieties. Rice and wheat, two other major food crop plants, have similarly been transformed from their wild progenitors. Modern wheat is, in fact, an interspecific hybrid and polyploid, with 3 different genomes. We have modified virtually all plants we now use for food, selecting mutations that make the edible portions larger, less toxic, easier to harvest and more attractive in flavor.

Molecular biology entered agriculture in the last decades of the 20th century and the cultivation of genetically modified crops on a commercial scale began in 1996. By 2008, roughly 10% of cropland was planted in GM crops: transgenic crops were grown on more than 330 million acres in 25 countries by more than 14 million farmers, 90% of whom were small-holder, resource-poor farmers (James, 2009).

When Malthus penned his essay, the human population of the world was about a billion. Science-based agriculture supported a tripling of the global population by the middle of the 20th century and another doubling in the second half of the century. Remarkably, the fraction of humanity suffering from chronic hunger declined from half to a sixth, even as the population doubled from 3 to 6 billion. That's the good news.

The bad news is that this success has come at a price. The planet's forests and prairies have given way year by year and decade by decade to much simpler agricultural ecosystems virtually everywhere in the world. Complex ecosystems have been replaced by monocultures, often watered from fossil aquifers. This is where we are today. The loss of biodiversity is already at catastrophic levels and continues to accelerate. Moreover, it is not confined to species on land. The overuse of fertilizers has resulted in the eutrophication of rivers, lakes and coastal seawater, making waters uninhabitable for many aquatic and marine organisms.

Unfortunately, there's no going back. Nostalgic calls to return to pre-scientific agricultural methods—often known as organic agriculture—are just that: nostalgic. Because of its reliance on biological nitrogen fixation, organic agriculture could at best feed a human population half of our current roughly 7 billion.

The global food crisis of 2008 took many people by surprise. Unfortunately, it was not a crisis in the usual transient sense, but rather a tipping point and a harbinger of things to come. Continuing growth of the human population and its increasing demand for meat, diversion of grain to biofuels, three decades of declining investment in agricultural research, combined with widespread drought that year to trigger a sudden upward spiral in the cost of the basic staple grains that feed humanity and its animals.

Prices came down somewhat the following year, but appear to be on the rise again because of extreme heat in parts of the world and extraordinary flooding in other parts. Although we are just beginning to assess the likely impact of climate change on agriculture, the summer of 2010 is consistent with climate scientists' predictions for a changing climate. Such extremes of temperature and storm activity are anticipated to become increasingly common with each passing decade. By the end of the century, much of the world is predicted to experience summers hotter than the hottest summer on record. Indeed, some have set records this year at the end of just the century's first decade (IPCC, 2007).

Population experts anticipate that the planet's human population will expand by another 2–4 billion by midcentury (Cohen, 2003), but the amount of arable has not changed substantially in more than half a century (Land Commodities Report, 2009). As well, water is becoming a critical variable. Today, drylands comprise a bit more than 40% of land area and these are home to about a third of the world's human population. Climate scientists predict that many of the earth's most populous places will become both hotter and drier.

We face stiff challenges in our efforts to increase the food supply in the 21st century. We need to increase the tolerance of our current crops to heat, drought, flooding, salinity, pests and diseases. And we need to do it biologically, so that we reduce our reliance on toxic chemicals that kill organisms indiscriminately. We need to increase crop productivity while at the same time increasing nitrogen utilization efficiency so that we can reduce nitrogen and phosphorus pollution of air and water. We also need to increase current limits on photosynthetic efficiency—a tough task that scientists have yet to tackle seriously.

We also have to start thinking well outside of the box: domesticating new crops and develop new farming systems that use land now considered useless and water now considered unusable, all powered by sun and wind. We can't step back to methods that sufficed for a world of a billion people. Yet we must seek to incorporate the ancient wisdom of integrating the flow of nutrients from plants to animals and back to reduce nutrient pollution of land and water. We have to go forward using the best science available. What are the obstacles? Well, time for one. Population pressure and climate change are upon us: we have decades, not the centuries or the millennia over which we developed our current crops.

Money for another, developed countries invest vastly more in the health sciences than in agriculture, food and feed technology. And then there's the continuing controversy over using contemporary molecular methods to improve crops, called genetically modified (GM) or genetically modified organisms (GMO), despite their record of safety and efficacy.

GM crops have been in commercial production for more than a dozen years, are grown in 25 countries on more than 10% of all Earth's cropland by more than 14 million farmers. Of these, 90% are resource poor, small-holder farmers (James, 2009). Steep regulatory barriers were initially instituted because it was feared that GM crops would pose novel risks to biodiversity, as well as human and animal health. None of the many hypothesized risks have been realized. To date they remain hypothetical, while the benefits are both real and substantial. Moreover, they could be much greater if we could just bring ourselves to demolish the regulatory barriers we've erected around GMOs out of unfounded fear. Indeed, it is precisely biologically-based genetic modifications that are our best hope for simultaneously increasing crop productivity and decreasing the impact of agriculture on biodiversity through decreased use of fertilizers and toxic chemicals.

But we must also turn our attention to using science and technology to farm land considered inhospitable with water considered unsuitable for agriculture. Aquaculture is part of the answer. As practiced in many places today, aquaculture exacerbates the problems of nutrient pollution of water, but recirculating systems and integrated aquaculture and either hydroponics or conventional farming are rapidly being developed. Such integrated systems can be used both on land and in the sea to close the nutrient cycles. Improved methods of water reclamation and recycling and crops adapted to brackish water will be important. As well, the domestication of salt-tolerant plants, technically called halophytes, and the integration of saline agriculture with aquaculture on coastal deserts is an idea whose time has come. At the heart of such integrated systems is closing the nutrient cycle between plants and animals to drastically reduce the detrimental environmental impact of agriculture.

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12

Opportunities to Achieve Resource-Conserving Increases in Agricultural Production: Learning from the System of Rice Intensification (SRI)

Norman Uphoff

Summary

Sustainable development involving conservation of natural resources and equitable access that reduces poverty and food insecurity will become more attainable if we can produce more agricultural output with reduced inputs. The methods of the System of Rice Intensification (SRI) developed in Madagascar now being extended to other countries and other crops are showing that production can be increased with

- Reduced seed requirements by making large reductions in plant populations;
- Less water by stopping continuous flooding; and
- Reduced agrochemical inputs as organic inputs are increased and as crops become more resistant to pests and diseases. Also, crops with larger root systems are better able to resist adverse effects of climate change

This all sounds too good to be true, but the enhanced productivity of SRI's alternative methods for managing crops, soil, water and nutrients is giving farmers more productive phenotypes from practically all genotypes evaluated so far. This has been seen now in more than three dozen countries

across Asia, Africa, Latin America and the Middle East (http://ciifad.cornell.edu/sri/).

Introduction

Getting more productivity from our available resources will be needed for 21st century agriculture to meet the world's food requirements under conditions of production that are becoming foreseeably less favourable.

- **Land resources** continue to decline. By 2050 we will have only one-third as much arable land *per capita* as in 1950. Land degradation is accelerating and reducing both the quantity and quality of land through erosion, salinization, compaction, and loss of fertility. Also, productive area is being lost to urbanization.
- **Water** will become a more limiting factor of production, both in its amount and in its reliability. Chemical and other pollution is diminishing water quality, and competing demands are constraining the availability of water for agriculture.
- **Climate change** is adding more constraints as 'extreme events' have more dire effects on agriculture than other sectors. High/low temperatures and increased/reduced rainfall can be disruptive, even disastrous for farming operations.
- **Energy costs** will probably be considerably higher in this century than the preceding one. This will make large-scale mechanized production and long-distance trade in agricultural products less economically profitable.
- **Environmental considerations** will constrain current exploitative practices because agriculture will increasingly have to account for its negative externalities

There are two main strategies for intensification to achieve agricultural production objectives:

1. **Intensification of *inputs*** – more water, chemical fertilizers, agrochemicals, etc. – with modifications in *genotypes* through breeding programs to raise the productivity of inputs. The Asian Green Revolution followed this strategy using high-yielding varieties supported by greater investment of resources to achieve higher returns
2. **Intensification of *management*** – investing more knowledge and skill in improving the combinations of inputs (kind, amount, sequence, timing, etc.) – in order to capitalize on biological processes and already-existing potentials. The aim is to achieve more productive phenotypes from any and all genotypes. One always wants to start with the best available varieties, to be sure, but they are only part of the productivity equation

Figure 1. Rice plant (cv. Ciherang) having 223 tillers, grown with SRI methods in Panda'an, East Java, Indonesia, and presented to author in 2009. (Picture by author.)

This latter strategy has been characterized as 'sustainable intensification' (Royal Society, 2009) and as 'low-input intensification' in a study commissioned by the European Parliament (Meyer, 2009).

Input intensification in the 20th century has been driven particularly by the disciplines of engineering, chemistry and genetics, while management intensification is guided more by biological and ecological knowledge. The latter involves a 're-biologization' of agriculture that draws on frontier advances in microbiology, soil ecology, plant physiology, phytohormones, and epigenetics, as discussed in my other paper for the proceedings (pages 00–00).

Experience with SRI is directing attention to the management of rice plants' environments and to comprehending what activates SRI-grown plants' expression of previously unrealized genetic potential. The rice plant shown in (Figure 1) above was grown by SRI farmers in East Java, Indonesia, from a single seed. It was presented to me during a visit in October 2009, so I have held it in my hands. I have also held in my hands, in Sri Lanka, a panicle of rice with 930 grains on it. (Unfortunately I could not take a picture of it because I had no camera with me; 200 grains would be considered a very good panicle, and 300 grains is considered remarkable.)

While it is true that this was the Sri Lankan farmer's best panicle, this does not detract from the evident potential for greater productivity that it represents, available for tapping by improving the way that plants, soil, water and nutrients are managed, to elicit bigger and better root growth as well as a larger and more diverse soil biota. The farmer in this case, W.M. Premaratna, had been farming organically for 10 years, and this was his third year using SRI methods. He was capitalizing on the soil-plant-microbial interactions that are the foundation for this strategy for 'intensification,' promoted by management methods that change long-standing practices.

These results are admittedly hard to believe, since they diverge so much from usual experience, increasing production often by multiples instead of increments. It took me three years to accept that the results of SRI practices were genuine. CIIFAD, the institute at Cornell of which I served as director (for 15 years), was assisting in implementing a USAID-funded project in Madagascar, intended to help save the endangered rainforest ecosystems within Ranomafana National Park.

In the 1994/95, 1995/96 and 1996/97 seasons, poor households cultivating in the peripheral zone around the park—who learned to use SRI methods from the NGO Association Tefy Saina—had paddy yields averaging 8 tons/ha, four times more than their previous usual yields of 2 tons/ha. After seeing such results for three years, it was evident that this large difference was not due to measurement error; both averages were calculated by the same methods. From 1997, I became interested, first, in getting the new methods better understood and, then, getting them evaluated and demonstrated in other countries.

I learned subsequently that a French-funded irrigation improvement project had documented similar results over this same period on the High Plateau in Madagascar. From 1994 to 1999, within small-scale irrigation schemes assisted by the project, SRI use expanded from 34.5 ha to 542.8 ha—with no organized extension effort. The project's data showed SRI yields averaging 8.55 tons/ha, while average yields with farmer practice were 2.36 tons/ha and 3.77 tons/ha with 'improved' practice, using fertilizer, flooding and new varieties (Hirsch, 2000).

Such remarkable differences were subsequently reported from countries outside Madagascar. These were most impressive where small and poor farmers were involved, for whom four-fold increases in production could be transformative. In central Cambodia in 2006, LDS Charities assisted 146 rainfed rice farmers whose conventional yields averaged 1.06 tons/ha. By using SRI methods, they averaged 4.02 tons/ha (Lyman et al., 2007). In Aceh province of Indonesia, where the Catholic charity CARITAS introduced SRI methods in 2005 after the tsunami devastation, small-farmer paddy yields went from 2 tons/ha average to 8.5 tons/ha (Cook, 2009).

Not all increases are as dramatic as these, but 50–100% increases are reasonably common. They suggest that we are dealing with something that can probably be best understood with fresh eyes and fresh ideas, even as it needs to be (and can be) explained with methods and theory that are accepted in contemporary agronomic science (see below).

The System of Rice Intensification

SRI was developed in Madagascar in the 1980s, after two decades of observation and experimentation (Laulanié 1993). Although devised to improve the productivity of smallholders' resources (land, labor, water and very little capital), the insights and idea on which SRI is based are now being adapted to *upland* (rainfed) conditions where farmers have no irrigation and thus little control over water.

There are also *direct-seeded* adaptations and *zero-tillage* (raised bed) adaptations, so the system is still evolving and diversifying. Of perhaps most interest, the results seen with SRI management have prompted farmers and others in several countries to begin extending the concepts and techniques, with appropriate modifications, to *other crops* such as wheat, sugarcane, finger millet, and even vegetables.

SRI methods move away from input intensification in that they do not require farmers to adopt 'improved' varieties, buying new seed, or to purchase inputs like fertilizer and crop protection sprays. It is true that the best SRI yield results have been attained with hybrids or high-yielding varieties. Plant breeding can boost yield. But with SRI methods, farmers can get increased production from almost any variety, and often their preferred varieties command a higher price in the market because of consumer preferences. So it can be more profitable to cultivate local or traditional varieties with SRI methods. SRI makes conservation of rice biodiversity more tenable.

Using synthetic fertilizer together with SRI management does give higher yields as a rule. Indeed, SRI was developed by Fr. Henri de Laulanié, SJ, in the 1980s using chemical fertilizer at first—until government subsidies were withdrawn and fertilizer became too costly for the farmers with whom he worked. It was found that compost could raise yields even more than fertilizer, with less cash expenditure. Organic rice production thus can be more profitable even without premium prices. Further, while chemical applications can be used along with SRI methods to control rice pests and diseases, farmers commonly find that SRI plants organically grown have enough natural resistance to pest and disease damage (Chaboussou, 2004) so that agrochemical protection is not necessary or not economic.

These advantages from a farmer's perspective have not made SRI popular with promoters of 'modern' agriculture, however. There has been controversy (Dobermann, 2004; Sheehy et al., 2004) and some resistance even to evaluating SRI methods in a systematic way (Sinclair, 2004; Sinclair and Cassman, 2004). The prevailing paradigm expects higher yields to be attained by improving genotypes and increasing external inputs, so it is understandable that a strategy which just changes the management of plants, soil, water and nutrients would seem inadequate.

For some years, there were only observations of the differences that SRI practices induced in the phenotypical expression of plants' genetic potential to consider. The larger and healthier root growth on SRI plants was very evident and visible (Figure 2), and an accompanying increase could be seen in the number of tillers per plant (Figure 3). There are now are a number of well-designed and controlled comparative studies published in the peer-reviewed literature which confirm the field observations, going beyond documentation of changes in the numbers of tillers, size of panicles, and root system growth. These studies provide measurements of significant differences between SRI and conventionally-grown plants on for parameters like leaf area index, tiller angle, light interception, rates of root exudation, photosynthesis and transpiration, chlorophyll levels, water-use efficiency, nitrogen uptake, and delayed senescence, e.g., Mishra and Salokhe (2008), Lin et al. (2009), Zhao et al. (2009), and Thakur et al. (2010). Such research helps to explain the success of SRI methods which have been shown to improve rice phenotypes in dozens of countries across Asia, Africa and Latin America. The three most recent countries from which

Figure 2. Comparison of roots and culms of rice plants, same variety and age. On left is plant grown with recommended SRI methods; on right is one grown with conventional (flooded) practices. Color of the roots of plant on right indicates necrosis from lack of oxygen. (Picture courtesy of Bahman Amiri Larijani, Haraz Technology Development Center, Amol, Iran.)

Figure 3. Individual rice plant grown with SRI methods in Baghlan province, Afghanistan, which has 133 tillers at 72 days after transplanting. The farmer's yield on this field was 11.56 tons/ha. (Picture courtesy of Ali Mohammed Ramzi, Aga Khan Foundation-Afghanistan Program.)

SRI effects have been reported are Kenya, the Democratic People's Republic of Korea, and Panama.

Changes in the Management of Plants, Soil, Water and Nutrients

How are these differences in the phenotype achieved? By changing certain practices that have long prevailed in rice culture. They are summarized as below, with the caveat that the practices are not absolute or sufficient just by themselves. There are basic principles that justify each practice, and these principles are explained to farmers, not just telling them what practices to follow. Farmers are expected to make their own experiments, modifications and adjustments to their local conditions to get best results. We stress that SRI is not a technology with no 'transfer' expected. SRI is a knowledge-based innovation, not relying on material inputs (although a simple mechanical weeder that aerates the soil as it controls weeds is highly recommended). Accordingly, farmers' understanding is the key to SRI, not just doing the practices themselves.

SRI, in terms of practices, is represented by the following recommendations:

1. If establishing the rice crop through transplanting,[1] transplant <u>young seedlings</u> while still in the 2–3 leaf stage, usually 8–12 days old – usually seedlings 3–4 or more weeks old are used, which have lost much of their growth potential for tillers and roots.
2. Avoid <u>trauma to the roots</u> – transplant quickly and shallow, *not inverting root tips which halts growth* – conventional transplanting causes 'transplant shock' and suspends growth for 7–14 days.
3. Give plants <u>wider spacing</u> – <u>*one plant per hill*</u> and in <u>*square pattern*</u> to achieve the "edge effect" everywhere – rather than plant seedlings in clumps of 3–6 per hill, and space hills 10–20 cm apart *vs*. 25 cm or wider with SRI.
4. Keep paddy soil moist and mostly aerobic—rather than continuously flooded and saturated as is the common practice now.[2]

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1. Direct-seeding has become an option for SRI in some places, where farmers have adapted the other practices to this alternative method for crop establishment, to save labor. This opens up SRI application to much larger scale.
2. Note that the other SRI methods have been adjusted to unirrigated, rainfed rice production with good results.

5. Actively aerate the soil as much as possible with mechanical implement (rotating hoe or conoweeder) – rather than weed by hand or use chemical herbicides.
6. Enhance soil organic matter as much as possible – while fertilizer can be used with the other SRI methods, the best SRI results have come from compost applications

These methods are not all that is required for rice production, but rather are the main changes made with SRI. Land preparations is necessary, with good land levelling advised when young seedlings are use. The nursery should be dry (not flooded), like a garden, but seedlings, much reduced in number, can even be raised on small trays, for easy transport to the field. Careful seed selection is possible when the seed rate is reduced by 80–90%, and this contributes to higher yield.

Results in a Variety of Agroclimatic Environments

One of the initial verdicts on SRI was that if it has merit, this applies only under certain growing conditions, making SRI a 'niche innovation' (Dobermann, 2004). Yet, the innovation has been found to raise yields in a wider variety of circumstances and also to be adaptable to larger scale.

- *Indonesia:* The results obtained by small farmers in the tropical environment of Aceh were reported above, getting 8.5 tons/ha where they had previously produced 2 tons/ha (Cook, 2009). In Eastern Indonesia, an evaluation of SRI methods over 9 seasons under a large Japanese-aided irrigation management project found that farmers (N=12,133) had averaged 78% higher yields with 40% less water and a 50% reduction in their fertilizer use (Sato and Uphoff, 2007).
- *Bhutan:* An agricultural extension agent assigned after graduation from the College of Renewable Natural Resources, where he had learned SRI methods, reported on a series of trials on farmers' fields in a mountainous district, Deorali Geog, in 2009. Standard practice gave 3.6 tons/ha; SRI methods with random spacing gave 6 tons/ha; SRI with 25x25 cm spacing gave 9.5 tons/ha; and these methods with 30x30 cm spacing gave 10 tons/ha (http://ciifad.cornell.edu/sri/countries/bhutan/bhDorjiDaganaRpt09.pdf).
- *Afghanistan:* The Aga Khan Foundation introduced SRI in Baghlan District in 2007. The initial yield was low because planting was one month late, and the northern location and high elevation made for a short growing season. In 2008,

six farmers, impressed by the tillering they had observed the year before, tried the new methods, and their yield was 10.1 tons/ha compared with 5.4 tons/ha on adjacent comparison plots. In 2009, the 42 farmers who used SRI methods averaged 9.3 tons/ha, compared to 5.6 tons/ha yields on their comparison plots using their usual methods. The six farmers in their second year averaged 13.3 tons/ha compared to the 8.7 tons/ha that the 36 first-year SRI farmers got. (http://ciifad.cornell.edu/sri/countries/afghanistan/AfgreportAKF_APMIS09.pdf).

- *Mali:* In 2007/08, the NGO Africare did first SRI trials with farmers on a small scale in irrigated perimeters in the Timbuktu region, on the edge of the Sahara Desert. The yield was 8.98 tons/ha, 34% more than the best yield obtained with other methods. The next year, 12 villages nominated 5 farmers each to evaluate SRI methods in a systematic way with side-by-comparison plots. These farmers' SRI plots produced 9.1 tons/ha compared to 5.49 tons/ha with their best methods; neighboring farmers in averaged 4.86 tons/ha (http://ciifad.cornell.edu/sri/countries/mali/MaliAfricare%2008and09.pdf). We see these kinds of gains in productive very often with SRI management, even under unfavourable local conditions.

Growing Support and Acceptance

SRI was initiated as a civil society innovation; however, it has been gaining support from a wide range of institutions: governments, donor agencies, universities, research institutions, foundations, international and grassroots NGOs, community organizations, and private sector. That productivity gains such as those reported above are achieved with *lower* water requirements in a world where water is becoming a more critical constraint has evoked growing interest in governments and donor agencies:

- For example, on the eve of a visit to India, the World Bank president wrote: "Everyone cites India's Green Revolution. But I'm even more intrigued by what is known as SRI, or system of rice intensification, and I know this is also an area of interest for [Prime Minister] Manmohan Singh. Using smart water management and planting practices, farmers in Tamil Nadu have increased rice yields between 30 and 80 per cent, reduced water use by 30 per cent, and now require significantly less fertilizer. This emerging technology not only addresses food security, but also the water scarcity challenge that climate change is making all the more dangerous. These are all lessons for our world." Robert Zoellick, *Hindustan Times*, December 2, 2009[1].

- Speaking at an SRI harvest festival in Cianjur in July 2007, the President of Indonesia, S.B. Yudhoyono, observed: "There are many methods of increasing rice production, and certainly they increase the production of rice, but it is the intervention of too much chemical fertilizer that we are witnessing. The result is an increase in productivity, but then the environment is badly damaged. ... this SRI method, according to my observation, fulfills both purposes: productivity is increased, and at the same time the environment is saved." (Speech is reported on his website at: http://www.presidenri.go.id/index.php/fokus/2007/07/30/2084.html; with English translation: http://ciifad.cornell.edu/sri/countries/indonesia/indopresident073007.pdf).
- The Worldwide Fund for Nature (WWF) in a collaborative program with ICRISAT on Food, Water and Environment has been supporting evaluations and dissemination of SRI methods in India to reduce conflicts over water there between agriculture and natural ecosystems (see http://assets.panda.org/downloads/wwf_rice_report_2007.pdf). The two organizations are also jointly promoting an adaptation of SRI concepts and practices to sugarcane, which is a heavy consumer of water and user of agrochemicals. See manual on applying SRI ideas to sugarcane: http://assets.panda.org/downloads/ssi_manual.pdf

Conclusions

Being able to raise agricultural production with lower demands on land, labor, capital and water opens new opportunities for 21st century agriculture. This is all the more important as climate changes are likely to lead to greater abiotic and biotic pressures on crop production. So far, SRI plants have been found to be more resistant to the effects of drought, lodging (storm damage), cold spells, and losses from pests and diseases.

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1. The Prime Minister endorsed "better agronomic practices like the System of Rice Intensification method of rice cultivation" in an address to senior Cabinet members and Chief Ministers of India's states on reducing food prices (April 8, 2010). See World Bank Institute website: http://info.worldbank.org/etools/_docs/library/245848/index.html and also the World Bank's India website on its positive experience with SRI in Tamil Nadu state of India:: http://www.worldbank.org.in/WBSITE/EXTERNAL/COUNTRIES/SOUTHASIAEXT/INDIAEXTN/0,,contentMDK:21789689~menuPK:64282138~pagePK:41367~piPK:279616~theSitePK:295584,00.html

There could even be some net reduction in greenhouse gas emissions with SRI conversion to aerobic soil conditions not relying on heavy applications of inorganic nitrogen. Methane emissions from rice paddies can be reduced by stopping their flooding, and so far, evaluations have indicated that there are not offsetting increases in N_2O emission (Yan et al., 2009).

SRI methods have validated now in 41 countries, but they will not be appropriate under all agroecosystem conditions, e.g., where soils cannot be maintained in mostly aerobic conditions, or where there is limited biomass availability for compost making (although chemical fertilizer can be used with the other SRI methods). While SRI was initially considered labor-intensive, farmers are finding that its methods can become labor-saving, once mastered. Also, mechanization of different SRI operations is now starting to be used to reduce labor requirements (http://www.google.com/search?hl=en&source=hp&q=FarmAll+MSRI+Pakistan). So, the main obstacles to further adoption and spread continue to be attitudinal than material. Like all innovations, SRI should be put to empirical tests. So far, when the methods are used as recommended with some experimentation and adaptation (part of the recommendation), they have proved to be productive under a wide range of circumstances.

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13

Future Priorities for Enhancing Global Food Security

Rajul Pandya-Lorch

Summary

Food insecurity remains a pervasive problem in developing countries, and it will be further challenged in the coming decades by rising population, demographic shifts, increased agro-ecosystems vulnerability, and climate variability. To address potential challenges and take advantage of opportunities for enhancing food security and improving nutrition, priorities should be clearly set. Lessons from proven successes in agricultural development in the past should inform future priorities for reducing hunger. Sustained investments in agricultural science and technology and complementary areas are especially critical for success in agricultural development. Continued investment in these areas needs to be accompanied by new modalities for improving food quality and human nutrition such as rebuilding trust in food markets, innovating for more efficient use of natural resources, climate change mitigation and adaptation, and enhancing synergies between agriculture, nutrition, and health.

Introduction

Food insecurity, particularly in developing countries, remains a pervasive problem that faces humanity. Since the mid-1990s, the number of hungry people in the world has been increasing and has reached a record high of more than 1 billion in 2009 (FAO 2009a). Even though there has been some progress in enhancing global food security, hunger remains severe in many developing countries. According to IFPRI's 2009 Global Hunger Index—a combined measure of the proportion of undernourishment, child undernutrition, and child mortality—twenty-nine countries, mostly in Sub-Saharan Africa and South Asia, exhibit 'alarming' or 'extremely alarming' levels of hunger (Figure 1). The first Millennium Development Goal of halving hunger has seriously gone off-track. The number of hungry people needs to decrease by 73 million per year to reach the goal by 2015 (Fan 2010).

The recent hike in food prices has contributed to rising food insecurity through the deterioration of diet quality, increasing micronutrient deficiencies, and excessive food market volatility. Since poor people spend about one-third to three-quarters of their budgets on food, they have limited capacity to adapt when prices increase and wages do not adjust accordingly (von Braun 2008). To cope with food price hikes, they decrease food intake and consume less nutritious diets that provide important micronutrients such as Vitamin A, Iron, and Zinc. The resulting harmful impacts on nutrition and health have irreversible life-long consequences, especially for vulnerable groups such as women and children (Hoddinott et al. 2008). Increasing food price volatility, trade restrictions, stock-piling, and speculation caused serious harms to the food security of vulnerable groups and the productivity of smallholder farmers. This led to distrust in markets by all actors along the global food value chain.

Pressures on food security such as population growth, demographic shifts, increasing land and water constraints, and climate change put additional demands on food production systems. Looking forward, it is expected that fewer people will grow their own food in 2050, as the rural labor force shrinks (FAO 2009b). In addition, as food markets become more closely integrated, food price volatility will be transmitted farther and faster. The complexities arising from a combination of these pressures has renewed the attention of policy markers towards enhancing global food security.

This paper will first provide an overview of some of the forces that influence food security and agricultural systems. Next, drawing on IFPRI's project 'Millions Fed: Proven Successes in Agricultural Development' (Spielman and Pandya-Lorch 2009), it will examine lessons from successes in agricultural development which have led to tremendous gains in

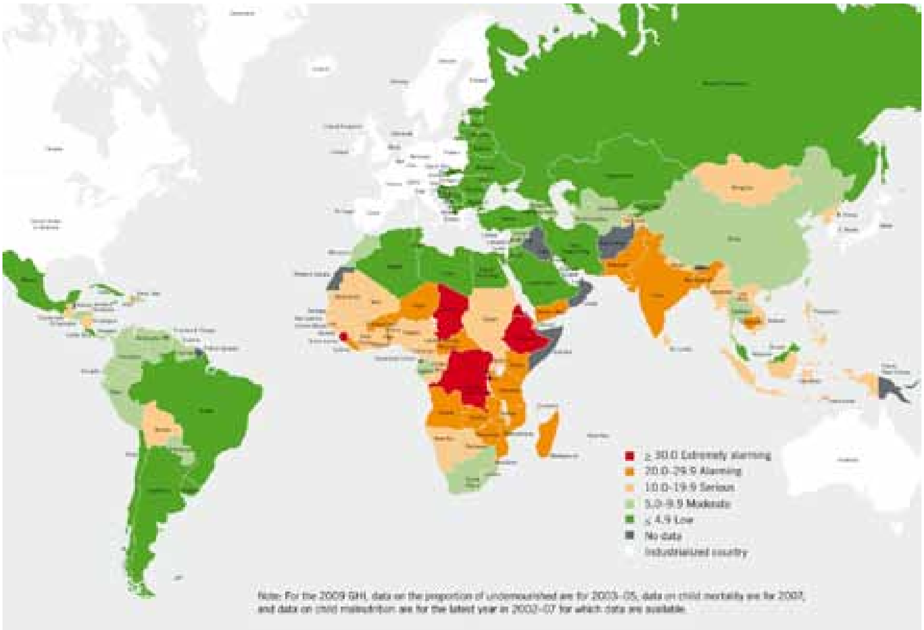

Figure 1. 2009 Global Hunger Index: Severity by country. Source: von Grebmer et al. 2009.

efforts to reduce global hunger. Based on these lessons, the paper will outline recommendations to guide future priority-setting in agricultural development. In addition, it will suggest new modalities for improving food quality and human nutrition. Conclusions follow.

Pressures on global food security

New complexities in the global food and agriculture system are putting enormous pressure on food security. Ensuring food availability, stability, access, and utilization is increasingly a more challenging task with population growth, demographic shifts, increased land and water constraints, and climate variability. By 2050, world population is expected to reach 9 billion, with predominant growth coming from urban areas and developing countries (United Nations 2008; FAO 2009b). The urban population in 2050 is expected to double, compared to 2007 (United Nations 2007). Expanding population accompanied by rising incomes as well as changing demographic patterns and consumer preferences present important ramifications for world food supplies. Rural-urban migration, for example, is increasing food demand and changing the quality and diversity of food consumed. In urban areas, shifting consumption patterns from staple foods to more high-value foods such as fruits, vegetables, meat, and dairy are on the rise (Gulati et al. 2007). Consumers are also increasingly concerned about food safety and demanding more processed and convenience foods.

Growth in world population also has large impacts on land and water resources required for agriculture. According to Rosegrant et al. (2009), water availability in the world, for instance, is estimated to decrease by 30% from 2000 to 2050 as a result of population growth. Climate variability increasingly puts additional pressure on land and water resources as well as food security. Climate change poses significant threats for food production with higher and more variable temperatures, changes in precipitation patterns, and increased incidence of droughts and floods. IFPRI estimates show that as a result of climate change, global production of wheat and rice, important staple foods in the developing world, is expected to be 27 and 14% lower in 2050 compared to 2000 (Nelson 2009). In addition, world food prices and child malnutrition are expected to be higher in all developing regions in 2050. Low-income countries and poor people that depend on agriculture and have limited capacity to adapt to climate change will be disproportionately hurt.

Lessons from past successes in agricultural development

It is important to remember that despite the serious challenges, there are also important opportunities for enhancing food security. Learning from proven successes in agricultural development and hunger reduction in the past is essential for preparing for food security challenges and opportunities in the future. IFPRI's Millions Fed project has rigorously assessed policies, programs, and investments that have made substantial contributions to reducing hunger in the past five decades (Spielman and Pandya-Lorch 2009). Through in-depth analysis of 20 selected case studies (Figure 2), the project identified key drivers of big successes in developing countries. These drivers include: (i) investment in agricultural science and technology, (ii) investment in complementary areas, (iii) promotion of strong private incentives, (iv) cooperation and collaboration, and (v) experimentation and evolution.

Past successes in agricultural development show that public investment in agricultural science and technology is vital to successes in agricultural development across the developing world. It is essential that this investment is sustained, despite competing demands for resources and long lead times for new technologies. To make a real impact on hunger reduction, investment in science and technology needs to be accompanied by sustained public investment in complementary areas of agricultural development such as irrigation, rural roads, education, and market infrastructure. Private sector investment in agriculture is also needed for agricultural development and hunger reduction, and needs to be encouraged by the right set of policies. In addition, it needs to be ensured that markets provide accurate and timely price signals to private sector actors. Cooperation and collaboration between diverse actors in the food and agriculture system—from research institutes and government agencies to community-based organizations and private companies—is also an important element of success in agricultural development. Last but not least, local step-by-step experiments that allow for learning, adaptation, evolution, and scaling up is important for agricultural development, and should be actively encouraged.

Figure 2. Proven successes in agricultural development: Case studies. Source: Spielman and Pandya-Lorch 2009.

Future priorities for enhancing food security

To address potential challenges and take advantage of opportunities for enhancing food security and improving nutrition, research priorities should be clearly set. Past successes in agriculture can provide valuable insights for future priority-setting. Key identified drivers of successes in agricultural development should remain a priority. Yet, while investing in agricultural development is extremely important, it is not sufficient for ensuring food security. Research on new modalities is also needed to ensure that adequate and nutritious food is available for people to live healthy and productive lives in the future. These new modalities include:

- **Rebuilding trust in food markets.** Actors at the global, regional, and national level need to take concrete steps to rebuild trust in food markets by eliminating excess volatility and ensuring open and transparent trade. These could include innovative structures for managing food supply and completing global trade negotiations.
- **Innovating for more efficient use of natural resources.** The rising competition for land and water as well as the degradation of environmental assets in many developing countries call for innovations in natural resource use. In addition, existing technologies such as water harvesting, minimum tillage, and integrated soil fertility management should be more widely adopted.
- **Climate change mitigation and adaptation.** A combination of adaptation and mitigation strategies is needed to alleviate the threat climate change will pose on the food security of poor people in developing countries. Due to its important role in mitigation and adaptation, agriculture must also be more effectively incorporated in climate change negotiations (von Braun and Pandya-Lorch 2009).
- **Enhancing synergies between agriculture, nutrition, and health.** Exploiting the synergies among agriculture, nutrition, and health can lead to large improvements in food security. These synergies need to be more closely studied, lessons from best practices should be shared and applied, and policymakers and practitioners working in these areas need to work closer together.

Conclusion

Enhancing global food security will become a harder task with the increasing complex interactions of global challenges such as population growth, demographic shifts, increased agro-ecosystems vulnerability, and climate variability. Past successes in agricultural development can provide valuable insights on effective ways to accelerate progress in reducing hunger. Lessons from these successes need to be applied and adapted to inform future priority-setting in agricultural development. As identified by IFPRI's Millions Fed project, the elements critical for successes in agricultural development include sustained investments in agricultural science and technology, irrigation, rural roads, education, and market infrastructure; promotion of strong private incentives; cooperation and collaboration; and experimentation and evolution. However, the causes of hunger and malnutrition are complex and require comprehensive solutions that go beyond agriculture. To ensure that adequate and nutritious food for people is available to live healthy and productive lives, new modalities for improving food security should be developed.

They should cover areas such as rebuilding trust in food markets, innovating for more efficient use of natural resources, climate change mitigation and adaptation, and enhancing synergies between agriculture, nutrition, and health. More research on these modalities is needed to ensure that clear priorities for food security policies are set at the global and national level.

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14

Increasing Cereal Nutritional Quality and Yield

Swapan Datta

Summary

Malnutrition is a severe problem in developing countries. Iron and vitamin-A deficiency affect millions of people, particularly women and children in the countries of Asia, Africa and on other continents. Iron deficiency is the most common nutritional problem in the world; 3.5 billion people are iron-anemic. Vitamin-A deficiency (VAD) causes symptoms ranging from xerophthalmia to keratomalacia, and can lead to total blindness. It is often claimed that enough food is produced globally to feed everyone, but in reality, 1 billion people who live on less than US$1 per day are starving or malnourished (1). Cereals and particularly rice serves as a staple food for 2 billion people and is also the primary food, providing 40–60% of the total calorie intake. Hence, biofortified cereals including rice and maize producing provitamin A and storing high iron in seeds would be an attractive yet alternate strategy for alleviating malnutrition. Ever since the advent of agriculture, there has been a need to improve crop plants (cereals) for higher productivity, better quality and to satisfy changing human preferences. This need is more acutely felt today and particularly in the developing world where the population is continuing to increase. Traditional plant breeding since the incorporation of Green Revolution have been very successful and have helped provide the volume of food required to allow the world population to grow to its present six billion (Borlaug 2009). Breeding efforts have provided us with remarkable diversity among various crop species and even some new crop species like

triticale and also introduction of new genes from wild species. However, the recent trends in crop productivity indicate that traditional methods alone will not be able to keep pace with the growing demands for food, fiber and fuel. The yield increases have hit a plateau or have fallen below the rate of population increase in many food crops. Farmers in south and south-east Asia must consistently produce an extra 30% more cereals and particularly 6.7 million tonnes of unmilled rice every year, without fail just to maintain current nutrition levels. Biotechnology offers a challenging role to reduce the gap of yield improvement. And this task does not become any easier with diminishing land and water resources. How do we convince policy makers of national governments to take the advantage of the combined green and gene revolution to reach most farmers whose livelihood can be improved by such knowledge based intensive technology? This task poses many challenges and reward for human welfare. Plant biotechnology particularly transgenics and molecular breeding can help plant breeding efforts to meet these new challenges in a sustainable way.

Introduction

Traditional plant breeding methods have been very successful and have helped provide the volume of food required to allow the world population to grow to its present six billion. Breeding efforts have provided us with remarkable diversity among various crop species and even some new crop species like triticale and also introduction of new genes from wild species (Brar and Khush 1997). However, the recent trends in crop productivity indicate that traditional methods alone will not be able to keep pace with the growing demands for food, fiber and fuel. The yield increases have hit a plateau or have fallen below the rate of population increase in many food crops. Farmers in south and south-east Asia must consistently produce an extra 30% more cereals and particularly 6.7 million tonnes of unmilled rice every year, without fail just to maintain current nutrition levels. Biotechnology offers a challenging role to reduce the gap of yield improvement (Hossain et al. 2000; Phillips, 2000; Khush 2001). And this task does not become any easier with diminishing land and water resources. Plant biotechnology and in future Nanotechnology can bolster plant breeding efforts to meet these new challenges in a sustainable way (Helmke and Minerick 2006). Plant biotechnology will dominate the 21st century for agriculture and human welfare. Plant genetic engineering has revolutionized and supplemented conventional plant breeding in crop improvement. Apart from broadening the genetic base, marker assisted breeding and transformation technology have helped improve the crop productivity, plant protection, and nutrition. Here we summarize some significant developments and achievements in the field of biotechnology and particularly in gene technology that accelerate designing the crop yield and enhance nutrition cereal crop.

Genomics and Cereals

Genomics implies DNA sequencing, the routine use of DNA microarray technology to analyze the gene expression profile at the mRNA level, and improved information tools to organize and analyze such data. Genomics-based strategies for gene discovery, coupled with the high-throughout transformation process, will accelerate the identification of candidate genes. The recent reports on rice genome sequencing by Monsanto, International Rice Genome Sequencing Project (IRGSP), Beijing Genome sequencing (BGI) and Novartis and with completion of genome sequencing of Arabidopsis will accelerate gene discovery and such crop improvement further. The genome sequencing work on wheat, barley and maize is on progress.

Genetic Transformation of Plants

With dramatic progress in the improvement of the transformation techniques, more than 50 different species of transgenic plants have been produced both from monocots and dicots and some (including cereals) are under field experiment world wide (James, 2009). A selective description of development of biotechnological tools, biological intervention and products development has been enumerated.

Transgenics in Stabilizing Production

A considerable proportion of the crop produce is lost due to biotic and abiotic stresses. Conventional breeding, which has often exploited the natural variablility in a species, has produced crop varieties with built-in resistance to several of these stress agents. However, in instances where the natural variability is limited or non-existent altogether, transgenic breeding could be a viable and an alternative solution. Transgenic plants that are tolerant to biotic agents like insect pests, and disease agents like viruses, fungi and bacteria have been produced, although only insect and virus resistant transgenic crops have been widely commercialized. Weeds can also significantly reduce crop yields. Transgenic crops with built-in resistance to broad action weedicides have also been commercialized in many countries. These transgenic crops allow the spraying of the weedicide in a standing crop. The weeds are killed while the crop remains unaffected. This makes weed control more effective and cheaper. Further it allows 'no-till' cultivation aiding in soil and water conservation. Abiotic stresses have been more difficult to tackle by transgenic approaches, but some of the recent developments hold great promise in this area as well.

Development of Homozygous Stable Lines

Isogenic lines using marker assisted breeding or homozygous lines using anther culture may accelerate crop breeding and stabilizing the improved traits. Since the pioneering report of anther culture published by Guha and Maheshwari in 1964 many researchers around the world made significant contributions in crop improvement (review, Datta 2005, 2007). The impact of this technology has now been well appreciated and utilized in marker assisted population studies, gene tagging and transgenic breeding.

Plant protection

Insect resistance

Transgenic crops with built-in plant protection can be cited as one of the exemplary success stories of agricultural biotechnology. The transgenic *Bt*-varieties are in many ways better than using *Bt* as a spray formulation. In the *Bt*-transgenics, the protein is expressed in all tissues at all times whereas the effectiveness of the sprays would be affected by lack of uniform coverage and instability of the *Bt*-protein, especially on exposure to sunlight. Considerable progress has been made in developing transgenic cereals with resistance to the target insect pests over the past decade. Though there have been many approaches to incorporate insect-resistance in transgenic plants, transgenic plants carrying the insecticidal protein gene from *Bacillus* *thuringiensis* (*Bt*) have been, by far the most successful. *Bt* is a soil bacterium that makes crystalline inclusions (*cry* proteins) during sporulation. These crystals dissolve in the alkaline environment of insect guts and release protoxin molecules that are processed by the gut proteases to give rise to active insecticidal proteins. These proteins interfere with the ion channel pumps and ultimately lead to the death of the insect larva that ingested the crystal. These proteins are quite specific in their host range (determined largely by ligand–receptor interaction) and this fact has been exploited in the development of transgenics tolerant to specific groups of insect pests. Over 50 different *cry* proteins have been characterized which have different target insect specificity.

The introduction of this product reportedly cut down chemical insecticide use by 40%. This was followed by the release of pest-resistant transgenic cotton and corn. This is an example of the potential of biotechnology to come up with a solution for combating a problem in a manner that is more environment-friendly. Among the cereals, maize was the first one to be transformed and field-tested with *Bt* gene exhibiting high level resistance to European corn borer (Koziel et al, 1993). After the first transgenic crop produced with codon-optimized and truncated *cry* gene, several reports have been accumulated in the recent past all over the world in developing transgenic rice carrying single or fused *cry* genes under different constitutive or tissue-specific promoters that showed cent percent resistance to stem borers and leaf folder under green house as well as natural field conditions (Datta et al, 1998; Tu et al, 2000a; Chen et al 2006).An important recent finding shows that *Bt* rice in field does not have any significant effect on non-targetted environmental friendly insects (Chen et al 2006). China approved the commercial release of *Bt*63 rice as safe for the environmental release and consumption.

However, there have been a few concerns regarding the use of *Bt*-transgenic crops, the two major ones being effect on non-target organisms and the possibility of the target insects developing resistance to the *Bt*-protein. Though *Bt*-crops have been under wide cultivation since 1995, there has not been any instance of the pest developing resistance. As a pro-active measure, several strategies for the Insect Resistance Management have been evolved as a package for cultivation of *Bt*-crops. These strategies include refugia (growing a small proportion of the area under non-*Bt* crop along with the *Bt*-transgenic crop), gene pyramiding and high dosage of the protein in the plant to prevent any insects escaping in the *Bt*-field. A recent study (Tabashnik et al., 2000) shows that the natural frequency of the recessive resistance alleles did not increase in spite of extensive cultivation of *Bt*-cotton between 1997 to 1999 and the *Bt*-cotton crop remained extremely effective against the pink boll worm.

Resistance to Fungal Diseases

Plant species deploy an assortment of defensive responses soon after infection or exposure to fungal infection. These responses involve the biosynthesis and accumulation of pathogenesis-related proteins (PR proteins, Datta and Muthukrishnan, 1999). Besides, there are resistance genes in the plants upstream the defense responses that recognize the avirulence genes in the pathogens, which otherwise is known as gene for gene hypothesis. There is a good deal of progress made in deployment of transgenic strategy for development of transgenic crops resistant or tolerant to fungal diseases utilizing these resistant (R) genes as well as overexpressing the PR genes (Lin et al 1995).

Combinatorial expression of multiple PR-genes along with the R genes could provide effective and durable resistance in crop breeding (Wenzel, 1985). Transgenes pyramiding conferring resistance to bacterial blight, sheath blight, stem borer has been achieved (Datta et al 2002; Narayanan et al 2004).

Resistance to Bacterial Infection

Considerable research effort has been directed to utilizing the resistance (R) genes in the crop breeding program including rice. Five different classes of R genes cloned from different plant species have been characterized and tested for their efficiency in conferring resistance against bacterial pathogens. Among these, the fifth class representing a map-based cloned *Xa21* gene from rice conferring resistance to *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) is the well studied one (Song et al. 1995). *Xa21* encodes a receptor like kinase consisting of leucine repeat regions (LRRs) in the putative extracellular domain and a serine-threonine kinase in the putatitve intracellular domain, thus indicating an evolutionary linkage with the other classes of R genes at the molecular level. By virtue of its wide spectrum resistance against bacterial blight, a serious disease of rice, *Xa21* is the first R gene to be transformed into rice. Subsequently several reports showed the broad spectrum resistance of transgenic rice with *Xa21* gene against diverse isolates from different countries, indicating the fact that a single cloned gene is sufficient to confer multi-isolate resistance (Tu et al. 1998; Tu et al, 2000b; Datta 2004; Laha et al 2008). The transgene *Xa21* followed Mendelian segregation (3:1) pattern in the subsequent selfing generation indicating single locus insertion.

Herbicide Resistance

Weeds are considered to be one of the major pests of several important crops including rice causing considerable yield loss. The chemical control of weeds through the application of herbicides poses threat to human health and the environment apart from the heavy costs involved (Pandey and Velasco, 1999). Engineering for herbicide tolerance is a new way of conferring selectivity and enhancing crop safety and production. Hence herbicide technology combined with transgenic approach might give farmers the avenue to modernize agricultural technology with reduced labor (like choice of crops for rotation or double cropping) in an environmentally friendly system shown in rice and wheat (Datta et al. 1992; Vasil et al 1992).

Drought, Salinity and Cold Stress Tolerance

Water deficit is the key cause of abiotic stress in crops. However, a minor water deficit results in a reduction in photosynthesis, while major deficits lead to complete inhibition of photosynthesis and the production of reactive oxygen species (ROS) such as superoxides and peroxides. These intermediates affect membrane integrity and cause severe impairment of several physiological processes and biochemical reactions. Modifying crops to tolerate unfavorable environmental conditions could improve productivity under hostile conditions and also could expand the area of land under cultivation. A variety of genes isolated from bacteria, animals and plants have been tested for their ability to confer stress tolerance in plants. These analyses to a large extent have been carried out in dicot model systems like *Arabidopsis* and *tobacco*. There are quite a few studies, which have tested various genes in other plants like rice, maize etc.

Production of transgenic plants that accumulate osmoprotectants (e.g. glycine betaine) and osmolytes has been a very popular approach to study tolerance to salinity, drought and cold stress. Osmolytes are low molecular mass molecules and could be quarternary amines, amino acids or sugar alcohols. Some plant species that have inherent tolerance to abiotic stresses have been shown to accumulate these osmolytes under stress. These molecules are known to raise the osmotic potential of the cell that could help it in combating water stress. They could stabilize membranes and other macromolecular structures.

CBF1/CBF3/DREB

Many cold-regulated (COR) genes have a common upstream regulatory motif called C-repeat. These are co-ordinately regulated by C-repeat binding factors (CBF). The same motif is also referred to as DRE (drought responsive element). Transcription factors bind to these motifs under stress and activate the expression of genes resulting in tolerance to the stress. Overexpression of the *Arabidopsis* transcription factor CBF1 using the CaMV35S promoter resulted in enhanced freezing tolerance. Expression of a master switch gene in an inducible manner to control stress-responsive gene expression could be a very valuable approach to engineer stress-tolerance in crop plants incuding rice (Shinozaki-Yahguchi and Shinozaki 2000; Datta et al 2010, MS, submitted). A similar work with transgenic wheat has been reported by (Pellegrineschi et al. 2004).

Improving Productivity

The primary goal of crop improvement has been to increase productivity. The first wave of transgenics has successfully addressed input traits like insect and herbicide resistance, to sustain the maximum yield potential of the crops. The second wave of transgenic varieties is expected to enhance output traits like yield. This could be achieved through improving the source strength by essentially increasing the net photosynthesis at the leaf level. There are many steps at which photosynthetic losses can occur - light harvesting, electron transport, carbon assimilation, partitioning of the photosynthate and respiration. Various approaches which could minimise these losses would be to alter canopy structure, improve light acclimation, improve photoprotection, incorporate features of C_4 photosynthetic pathway in C_3 crops (rice), alter stomatal responses, alter carbohydrate metabolism, delay leaf senescence, alter metabolite signalling, reduce respiration capacity and improve nitrogen economy etc (Ashikari et a. 2005;Bandyopadhyay et al. 2006). It is unlikely that achieving one of the above with a transgene would directly reflect in yield improvement. In the source strength to sink capacity continuum, all of the above play major roles. Understanding the effect of expression of some useful genes in photosynthesis and partitioning will give clues to the useful combination of alterations that could result in discernible increases in yield.

Exploiting Heterosis

Heterosis breeding is a proven way of increasing productivity in many crop species. However, in many grain crops the exploitation of heterosis hinges on the availability of a good male sterility and fertility restoration system. Over the past several decades, many cytoplasmic male sterility (CMS) sources have been successfully developed and used for hybrid seed production in various crop species, including rice. In many cases the non-availability of proper CMS sources and/or restoration systems have been a major limitation in the development of commercial F_1 hybrid varieties. Sometimes the lack of diverse cytoplasmic sources has given rise to concerns about cytoplasmic uniformity and the consequent genetic vulnerability to pest and disease outbreaks. All these point to a need to develop alternative male sterility sources and fertility restoration systems. Transgenic plants can address this need as has been demonstrated at least in a few instances.

One of the earliest and successful attempts to induce male sterility by genetic engineering involved the transfer and tissue-specific expresion of a 'toxin' gene that disrupted normal pollen development. The toxin gene in this case was from a fungal source, *Barnase*, which was made to express itself specifically in the tapetal tissue of developing anthers by using the tapetum specific promoter TA29 Pental, review, 2003). Several similar studies have been reported in different crops including oil seed rape (review, Pental 2003)

Nutrition-Cereal Crops

Since agriculture is the primary source of nutrients, and poor diets are a fundamental cause of malnutrition, it is indispensable to have nutrition-rich crops for solving the problems due to such deficiencies. Nutrional genomics will have a tremendous impact on the improvement of foods for human health (DellaPenna, 1999). Datta and Bouis (2000) have discussed the potential of biotechnology in improving human nutrition through the very recent breakthroughs in genetic engineering e.g., development of golden rice, iron-fortified crops etc.

Three different genes involved in the metabolic pathway, phytoene synthase and lycopene cyclase (*psy* and *lyc* cloned from *Narcissus pseudonarcissus),* phytoene desaturase *(crtI* cloned from *Erwinia uredovora)* have been introduced into rice through *Agrobacterium*-mediated transformation method that resulted in what is called as the 'Golden indica Rice' producing beta carotene, which ultimately is converted to vitamin A in the human body. Research is in progress globally to engineer these genes for production of transgenic indica rice with beta-carotene in different elite indica rice cultivars as well as other cultivars adapted to different developing countries (Ye et al 2000; IRRI, 2000; Datta et al 2003; Paine et al. ; Parkhi et al. 2005; Krishnan et al. 2009).

Similarly, iron deficiency leading to anemia that covers around 30% of the world's population, is prevalent in the developing countries. Mostly people get their daily iron requirement from vegetables. So increasing iron content in the plants by genetic manipulation would have a significant bearing on the human health. An iron storage protein gene, *ferritin* driven by constitutive 35S promoter, was successfully transferred to tobacco where the leaves of transgenics had a maximum of 30% higher iron than the non-transformed control plants (Goto et al, 1999), and in lettuce, the transgenics showed 1.2 to 1.7 times more iron content, enhanced early developmental growth, superior photosynthesis than the control plants.

In rice and wheat also the use of constitutive promoter resulted in higher iron content in the vegetative tissues, not the seed. However, *ferritin* gene placed under an endosperm-specific promoter, glutelin was expressed in the seeds (the target tissue) in Japonica rice (Goto et al, 1999). The iron content in the endosperm of transgenic rice was significantly higher than that of the non-transformant. All these studies used the *ferritin* gene cloned from soybean. Recently Lucca et al (2001) also observed increased iron content in the rice seeds transformed with *Phaseolus* ferritin gene.

Furthermore, since the endogenous phytic acid inhibit the iron bioavailbility, a heat-stable phytase from *Aspergillus fumigatus* was introduced into rice (Lucca et al, 2001), which increased the level of *phytase* by 130-fold sufficient enough to hydrolyze the phytic acid. In addition, as cysteine peptides are considered a major enhancer of iron absorption, endogenous cysteine-rich metallothionein-like protein was overexpressed in rice, which increased the cysteine residues by 7-fold (Lucca et al, 2001). The high *phytase* rice, with increased iron content and rich in *cysteine* peptide could potentially improve the iron nutrition in rice-eating population, and leaves the potential open to other crops too. RNAi technology is now being used in designer crop particularly in reducing phytate to increase the bioavailability of iron in rice (Ali et al. 2010)

Another gene, ferric chelate reductase (*FRO2*) that allows plants to uptake more iron in iron-deficient soil allows the possibility of co-integrating it with *ferritin*, *phytase*, and *cysteine* peptide genes for high iron uptake and storage in the plant, and bioavailability and absorption in the human body. At IRRI, transgenic rice has been produced with *FRO2*, and ferritin genes. Interestingly, transgenic plants showed 2–3 fold higher levels of iron in polished seeds along with enhanced levels of zinc. Further work is in progress on molecular breeding of transgenic rice combining both ferritin and genes for nutrition improvement (Datta et al, 2000 Vasconcelos et al 2003).

Another important essential but limiting amino acid in rice, lysine, that promotes uptake of trace elements is a potential candidate for the nutritional improvement of crops. Two bacterial genes, *dapA* and *lysC* from *Corynebacterium* has been shown to enhance the lysine about five fold in corn seed (Falco et al, 1995; Mazur et al, 1999). Lysine enriched rice has already been developed in collaboration with DuPont (Russel et al. unpublished data). Several food crops are now being developed with enhanced vitamin E, vitamin C, inulin, modified starch and amino acid profile, (Galili et al. 2002; Baisakh and Datta 2004).

Concluding Remarks

To meet the need of food and nutrition security, biotechnology, especially transgenics (GM crops) and Molecular Breeding (Marker assisted breeding) as complement to conventional breeding can improve farmer and consumer welfare in many ways. High yielding varieties of wheat and rice as a product of Green Revolution pioneered by Norman Bourlag saved millions of lives in Asia and continuation of Green Revolution in the manner of gene revolution is on progress which will help further increasing cereal-yield and value addition to biofortified foods. Sustenance of crop productivity through development of built-in disease and insect resistant crops, and/or increased crop productivity through novel genes, and the value-added crops would have significant impact in increasing the food supply, thereby help reduce the food prices for poor farmers. Recent significant achievements in plant genetic engineering for nutrition-rich crops would have the bearing in reducing the malnutrition of the people. Farmers will always benefit from growing them with guaranteed higher price. However, complete realization of such potential of biotechnology would take time with large investment in agricultural research and other public and on-farm infrastructure (Datta and Bouis, 2000).

Nonetheless, like any other technology, controversy surrounding GM crops are no exception in a heterogeneous society. Several concerns on different issues like food safety, beneficiaries of the technology, and conflict between plant varietal protection (PVP) and intellectual property rights (IPR) of gene and technology discovery, need to be addressed. Finally, successful product development needs extensive field trials and public understanding. Based on the experience of several successful field-evaluation of GM crops, it is predicted that gene technology combined with precise plant breeding and efficient crop management might provide the benefits people need. And, once the fruits of genetic engineering in agriculture reach small farms and industrial level operations, everyone can benefit from such development (Datta, 2000). Scientists must play sensible role in the society in convincing the policy makers in expanding further the application of biotechnology in modern agriculture and human welfare.

The technology is neutral and it must be utilized in greater cooperation with the technology owners/developers, agri-industry and the farmers' field of the developing and developed countries to stay in tune in the modern era of technology based modern Agri-practice to civil society including farmers. All people require food and the policy makers have more responsibility to take the right decision for its adequate productivity and to deliver it for a better world.

Acknowledgements

Thanks are due to the award of TATA Innovation Fellowship (DBT-GOI).

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15

Agricultural Biotechnology and Environmental Safety

Efffat Badr

Summary

There is an urgent need to produce enough food plants for the world's growing population. The challenge for plant breeders has been to transfer desirable genes into crops and to get them to express the traits. Biotechnology is the most rapid and effective way to transfer genes from unrelated species into crops. However, there are concerns about potential impacts arising from these transgenic crops. Systems of assessment and regulations have been established. Moreover there are several aspects of potentially positive effects that genetically modified plants could have on reducing the impact of agriculture on the environment and help maintain sustainability.

Introduction

Humans have used biotechnology for thousands of years. Perhaps the greatest impact of biotechnology has been in the area of plant agriculture. Plants have been cloned using various techniques of asexual propagation. Selective breeding resulted in producing new plant varieties that helped to feed the ever-growing population of the world. Recently, the advent of genetic engineering has greatly accelerated the process of plant improvement. Genetically modified (GM) plants have gained widespread use. Millions of acres of GM crops are produced each year. The major crops being soybeans, corn and cotton.

However, the availability of GM crops has created some unprecedented issues. A common concern with the release of any biotechnology-derived product is the effects it could have on the environment. Three major environmental questions were highlighted by recent reports from the National Academy of Sciences, United States might insect pests develop resistance to genetically engineered plant-incorporated protectants? Will these agents cause unintended damage to beneficial insects? Could engineered genes spread to nearly plants? In fact, all these issues can also be posed about non-engineered genes, but genetically engineered traits have been subject to controversy because they are presumed to be novel, without the benefit of years of accumulated wisdom about their impact. Agriculture and environment are two areas of science that must work together. More information about the benefits and drawbacks of genetically engineered crops are being provided every day. As a result of the lessons learned in this decade, the next decade of genetically engineered crops should prove to the even more successful and to change our world for the better.

Benefits of Agricultural Biotechnology

Fewer Pesticides

The first generation biotechnology crops, herbicide-and insect resistance plants, have been in commercial use since 1995 in the United States. This built-in protection reduces the need to apply conventional pesticides, especially the non-biodegradable ones, thus contributing to protecting the environment, just as the FAO emphasizes regularly.

Reduces Soil erosion

The worlds agricultural land is seriously degraded while the word population is increasing. Biotechnology crops can contribute to a decrease in erosion because harmful weeds are controlled while the crops thrive. This promotes no-till and conservation tillage system, thus helping to save the soil, conserve soil moisture and nutrients and preserve earthworm populations.

More Efficient Use of Farmland

There is urgent need to bring more land into agriculture. One way is to produce plants that can grow under substandard conditions. Native plants grow and thrive in hard climates; withstanding such conditions as drought, salinity, heat, cold or poor soil conditions. These genes have been successfully spliced into crop plants thus allowing agriculture in marginal land. Our research group has been exploring this possibility for Graminae species in Egypt.

More Food, Better Nutrition and Fighting Disease

About 790 million people in the developing world are currently undernourished. Fertilizers increase yields. However, besides costing money, they may also become pollutants. Through biotechnology, crop varieties can be enhanced to produce more food at lower costs by efficiently controlling disease, insects and weeds. A certain algae gene, inserted into crop plants can boost yield by almost one third because the new strain converts nitrogen fertilizers more efficiently. Higher yield of biotechnology crops have been reported by a number of resources including the World Bank and a joint consultation of FAO and WHO. Efforts are on the way to produce crops that can take in nitrogen directly from air rather than relying on fertilizers.

Moreover biotechnology can improve the nutritional value of foods, thus fighting disease and malnutrition. Plant-made pharmaceuticals that can deliver medicines and vaccines have been created. A new strain of rice that produces the protein that creates vitamin A and iron has been developed. Tomato with increased lycopene content (a component of Vitamin A) and canola oil with enhanced Vitamin E content are being produced. Nicotine-free tobacco may soon be available.

Environmental Concerns of Agricultural Biotechnology

Whenever new technology is introduced, there are concerns about its safety and effectiveness. Environmental concerns about the use of biotechnology in agriculture focus on the transfer of new genetic material to wild populations of plants and animals. Specifically are the concerns that herbicide-tolerant and insect-resistant crops will help create resistant strains of weeds and insects. Organic farmers are worried about Bt-technology because they use Bt-toxin on their crops as natural insecticide. The global exposure to insect population to this toxin creates a huge evolutionary pressure for the development of resistance. Other concerns of this technology are the effect on wildlife such as populations of beneficial insects. Gene flow from the created super-hardy plants may result in the development of invasive grass. A decrease in biodiversity is also possible and non-desirable.

The USEPA studies to date indicate that these concerns are not well founded.

Strategies and Regulations for Safety

Certain strategies are considered to reduce the possibility of gene flow. One such strategy is to plant crops that are not of closely related species. Farmers are also encouraged to cultivate a buffer zone around the herbicide-tolerant field, so the crop is less likely to mix with weeds. Another strategy is to plant what are called "refugia". This is a process in which non-insect-resistant plants are grown nearby. A population of non-tolerant insects is then available to mate with those that might develop resistance. The USEPA has taken measures to monitor the insect population and has required farmers growing GM crops to devote a fair portion of acreage to "refuge" or natural crops. Researchers are also working towards having the natural insecticide to be released at an appropriate time in the plants growth cycle, i.e. when the plant is at its most susceptible stage.

In order to ensure its safety, GM crops go through rigorous testing comprising several steps that usually take seven to ten years, before they are released. This is far more rigorous of a process than any conventionally derived food goes through.

In the United States, the USDA and EPA are the most involved agencies to determine if a food crop is safe enough to be grown in the environment. The USDA has the responsibility of reviewing data generated from field trails to determine whether a product or crop could have the potential to become a plant pest or cause any detrimental effects on the environment or wildlife. EPA focuses on the regulation of pest management. The development of a transgenic plant requires researchers to meet with one or more regulatory agencies to discuss the project in order to insure safety of the end product.

In Egypt, the National Biosafety Committee (NBC) was established in January 1995, for regulating environmental and food safety as well as variety registration of GMO's. The committee sets policies and standards concerning the use of genetic engineering and its product at the national level. The information requirements and risk assessment set by NBC are consistent with the Cartagena protocol on biosafety and the information requirements in other ports of the world. Currently under development is a Biosafety Act that implements Egypt's obligations under the Cartagena Protocol which deals with transboundary movement of GMO's.

Agricultural Biotechnology for Helping the Environment:

Agriculture is an important tool in the sustainability of our environment. Agriculture and the environment are two areas of science that must work together. Biotechnology plays a role in detecting and monitoring pollution; GM plants are sensitive tools for this purpose.

GM plants are now used for phytoremediation, selectively absorbing harmful material, including heavy metals, solvents, hydrocarbons, pesticides, radioactive metals, explosives, nitrates and crude oil. In order to decrease the amount of pollution in our waters and soils, scientists have determined ways that GM plants and bacteria in the soil can abort toxic wastes. Oil dissolving bacteria used to combat spills on beaches are used to clean up oceans and protect marine life. Bio-and phytoremediation tend to preserve topsoil and post-clean up costs as well as reduce environmental stress. However, phytoremediation techniques, although cheaper, are slower than chemical methods. Advances for newly engineered organisms will speed up the process. Potentially, plants can be modified to produce biodegradable plastic and coloured cotton.

Biotechnology pest-resistant crops, producing higher yield per acre will result in less pollution, decrease the extent of deforestation and feed the growing population, thus contributing to save the environment.

Biotechnology is also used for constructing gene-banks and to genetically characterize wild plants which can be used as genetic resources to improve economic plants. Techniques such as RAPD, RFLP, ISSR.. etc are used for this purpose. This is important for the establishment of data-base and molecular genetic documentation of wild plants. Molecular genetic characterization is important to protect intellectual property rights of wild plants. This is especially true for wild plants of the third world from where most novel genes for plant improvement are used. Our research group in Alexandria is involved in such activity.

Conclusion

For the next few decades, the biggest problem of our planet is to produce enough food plants. There is urgent need to get better yields, not only under good and bad conditions, but also in conditions that are completely hostile. Biotechnology offers tools to eventually solve the world's food problem. However, concerns about potential environmental risks of transgenic plants are raised and certain precaution seems to be justified. It is argued that these concerns exist both with biotech plants and those developed through conventional methods. In fact there are several aspects of potentially positive effects that GM plants could have on reducing the impact of agriculture on the environment Biotechnology will help feed the hungry, produce better food, revolutionize medicine and will make the environment cleaner. It is reassuring to know that the genes we modify, turn off/on or swap between organisms, biotechnology always uses the building blocks of life that GOD has bestowed upon us.

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16

The Quest for Nitrogen Fixing Cereals

Edward Cocking

Summary

Norman Borlaug has highlighted the need to extend the symbiotic nitrogen fixation of legumes with rhizobia to the world's major cereals, maize, rice, and wheat, to sustain the Green Revolution. In legumes, symbiotic nitrogen fixation occurs within cells of nodules that have been intracellularly colonized by rhizobia present in membrane-bound vesicles in the cytoplasm. The challenge of establishing a nitrogen-fixing symbiosis in cereals and other major non-legume crops is basically the challenge of establishing an adequate level of intracellular colonization and nitrogen fixation without necessarily the need for nodulation. We have investigated the interaction of *Gluconacetobacter diazotrophicus*, a non-nodulating nitrogen-fixing bacterium isolated from the intercellular juice of sugarcane, with the cereals maize, rice and wheat. We have shown that inoculation with a very low number of *G. diazotrophicus* (approx five per plant) results in extensive intracellular colonization of root meristems and progressive systemic plant colonization. These intracellular bacteria present in membrane-bound vesicles in the cytoplasm of the cells of roots and shoots express nitrogenase genes. We are investigating by nitrogen balances and ^{15}N methodology whether this non-nodular intracellular colonization by *G. diazotrophicus* results in symbiotic nitrogen fixation of benefit to plant growth. Field trials will need to be performed under a range of environmental and soil conditions to establish reductions possible in synthetic nitrogen fertilizer, while maintaining or increasing yields.

Introduction

In his Nobel Peace Prize acceptance speech in 1970 Norman Borlaug highlighted the need to extend the symbiotic nitrogen fixation of legumes to the world's major cereals, maize, rice and wheat to sustain the Green Revolution. 'In my dream I see green, vigorous, high-yielding fields of wheat, rice, maize, sorghum and millet which are obtaining, free of expense, 100 kilogram of nitrogen per hectare from nodule-forming nitrogen-fixing bacteria… This scientific discovery has revolutionized agricultural production for the hundreds of millions of humble farmers throughout the world, for they now receive much of the needed fertilizer for their crops directly from these little wondrous microbes that are taking nitrogen from the air and fixing it without cost in the roots of cereals from which it is transformed into grain…' He acknowledged that even though high-yielding dwarf and rice varieties were the catalysts that ignited the Green Revolution, chemical fertilizers, particularly synthetic nitrogen fertilizers produced from fossil fuel by the Haber-Bosch process were the fuel that enabled its forward thrust. Fritz Haber who had been awarded a Nobel Prize in 1918 for the chemical synthesis of ammonia from N_2 and H_2 (Erisman et al 2008), used for the production of synthetic nitrogen fertilizers, also like Borlaug had insights that were directed towards the future. Haber saw the potential of getting enough nitrogen fertilizer through the synthesis of ammonia not as the end point of a process, but only as a temporary solution to the problem of feeding the ever-increasing world population. He saw for the future other, more natural – today we would say more environmentally friendly-ways (Stoltzenberg 2004).

All of this was against the background that ever since it was established in 1888 that legume nodules fixed atmospheric nitrogen consistent efforts had been made to try to extend the intracellular symbiotic interaction of legumes with N_2-fixing bacteria to a wider range of crops, particularly the cereals. However, it was not until the isolation of the N_2-fixing bacterium *Gluconacetobacter diazotrophicus* in 1988 from the sucrose-rich intercellular spaces of sugarcane, and the demonstration that this bacterium fixes nitrogen inside sugarcane plants (Boddey et al 2008), did it become realistic to assess the extent of similar interactions with cereals. The quest for N_2-fixing cereals to fulfil Borlaug's dream is now increasingly focused on interactions with this bacterium.

Gluconacetobacter Diazotrophicus

This endophytic, non-rhizobial, bacterium colonizes sugarcane roots and shoots intercellularly and also the xylem with no evidence for intracellular colonization of living cells, and without nodulation (James et al 2001). This bacterium has many novel features that would facilitate its effectiveness in symbiotic nitrogen fixation if it could be established intracellulary in cereals, and also features that could facilitate its intracellular colonization of living cells. The UAP5541 strain of *G. diazotrophicus* is known to produce endoglucanase, endopolymethylgalacturonase and endoxyglucanase constitutively when grown on sucrose which could facilitate bacterial penetration of the primary cell wall of root meristematic cells, and subsequent endocytotic uptake of bacteria. *G. diazotrophicus* has a capability to excrete almost half of the N_2 it fixes in a form that is potentially available to plants; compared with most other microaerobic diazotrophs its ability to fix nitrogen is more tolerant to oxygen since it can achieve a flux of oxygen that maintains bacterial aerobic respiration, while not inhibiting nitrogenise activity, by utilising the path length of colongy mucoid levan polysaccharide between the atmosphere and the bacteria. It lacks nitrate reductase and can fix N_2 in the presence of 20 mM NO_3^-, and NH_4^+ causes only partial inhibition of its nitrogenase.

Requirements for Symbiotic Nitrogen Fixation

The most efficient N_2-fixing bacteria establish an intracellular symbiosis with plants in which they fix nitrogen inside the cells of their host utilising energy for nitrogen fixation supplied by plant photosynthesis. Within their host cells bacteria are separated from the plant cytoplasm by a membrane derived from the plant cell plasma membrane. In legume nodule cells rhizobia become internalised by a process resembling endocytosis (Figure 1) in membrane-bound vesicles (secondary vacuoles) within the cytoplasm. In these symbiosomes the N_2-fixing bacteria are surrounded by a plant-derived membrane, the symbiosome membrane. Whilst intracellular colonization of nodules occurs in legumes, nodule formation as such is not an essential requirement for the microbial symbiotic intracellular colonization of plants. In angiosperm Gunnera spp. the cyanobacterium *Nostoc* establishes intracellular symbiotic nitrogen fixation without nodule formation, and in the intracellular root symbioses of legumes and non-legumes, including cereals, with phosphate-acquiring arbuscular mycorrhizal fungi there is no nodulation (Cocking, 2005). Fully efficient use of atmospheric nitrogen

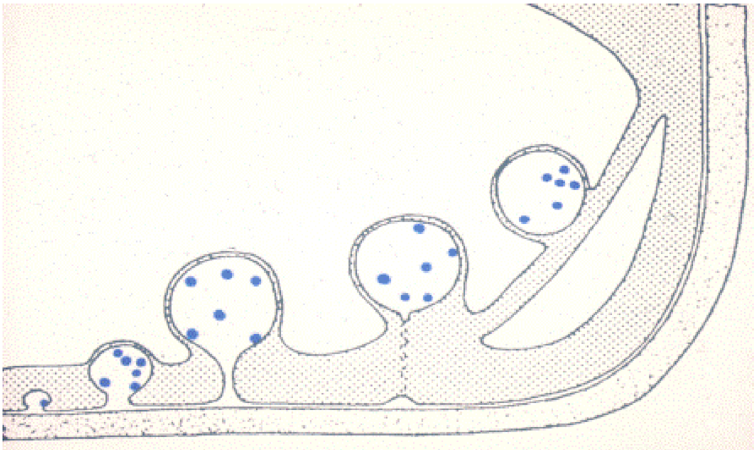

Figure 1. Conceptual diagram of the development of secondary vacuoles by endocytosis in plant cells. Invagination of the plasma membrane beneath the cell wall (shaded) results in the formation of a small vesicle that enlarges through the cytoplasm (dotted) protruding into the primary vacuole. If nitrogen-fixing bacteria (rhizobia or *G. diazotrophicus*; dots) penetrate through the cell wall they can become internalized by endocytosis and are then present in symbiosome-like secondary vacuoles in the cytoplasm surrounded by the symbiosome membrane derived from the plant plasma membrane.

(N_2) for plant growth can only be expected in endosymbiotic systems since only here can the prerequisites for symbiotic nitrogen fixation be fulfilled: reliable supply of metabolic substrates by the host photosynthesis providing sufficient energy and reducing conditions, protection against too high oxygen concentrations, transport of the N_2-fixation products to the host, development of membrane systems for bi-directional transport between host and endosymbiont and protection against competitive or antagonistic bacteria in the environment (Quispel, 1991).

The challenge of establishing a N_2-fixing symbiosis in cereals and other major non-legume crops is seen as basically the challenge of establishing an adequate level of bacterial intracellular colonization and nitrogen fixation without necessarily any need for nodulation. But why is there actually no such thing as a N_2-fixing plant and why do plants *have* to form a symbiotic association with N_2-fixing bacteria to be N_2-fixing? As highlighted by Postgate (1992), in terms of energetics, nitrogen fixation should present no evolutionary obstacle to plants. Eight molecules of ATP are required for every half N_2 molecules converted to NH_3 by bacterial nitrogenase and an additional 6 ATP are required as reductant making a need of 14 ATP per NH_3 produced. However, plants usually assimilate their nitrogen by the reduction of nitrate which requires 12 molecules of ATP to provide one molecule of NH_3; thus, nitrogen fixation is only marginally more demanding than nitrate reduction, in terms of energy consumption. Physiologically, the extreme oxygen sensitivity of nitrogenase proteins ought not to present a serious difficulty to plants. Anaerobic membrane-bound vesicular compartments are generally present in plant cells, and mitochondria have a low redox potential and adequate supplies of ATP. Indeed nothing in our present understanding of both the physiology and genetics of nitrogen fixation appears to raise any serious obstacle to the evolution of an autonomous nitrogen fixing plant. Postgate (1992) has commented that 'it remains surprising that no plant followed what seems to be the easiest path to independence of bacteria: to exploit bacterial solutions to both the genetic and physiological problems of nitrogen fixation by way of a 'diazoplast', a new organelle analogous to a chloroplast, acquired in a like manner by accretion of an endosymbiotic prokaryote into the plant's genome. The genetic obstacles to the emergence of autonomous nitrogen-fixing plants seem like the physiological obstacles, to be minor. So why has none appeared?' He suggests that plants never experienced the necessary selective pressure. He sees the requirement experimentally for the production of an autonomous nitrogen-fixing plant as 'giving evolution a push in a direction in which it is already poised to go'. A first step towards a N_2-fixing symbiosis in cereals, with the possibility of diazoplast formation, can therefore be seen as finding a bacterium that will establish itself intracellulary within plant membrane-bound vesicular compartments fixing nitrogen symbiotically. We selected the naturally occurring N_2-fixing bacterium *G. diazotrophicus* to try to achieve this key first step.

Inoculation of Cereals with G. diazotrophicus

We investigated the interaction of G. diazotrophicus (UAP5541) with seedlings of the cereals maize, rice and wheat. An aqueous suspension of G. diazotrophicus (5 colony forming units) was used for the inoculation of surfaced sterilised seeds germinated aseptically on Murashige and Skoog medium containing 3% (w/v) sucrose and vitamins but lacking growth regulators. Following inoculations with G. diazotrophicus containing a constitutively expressed gus A gene, the bacterial colonization of roots was visualised by light microscopy of the dark blue precipitate resulting from the degradation of the histochemical substrate X-GLUC by bacterial β-glucuronidase encoded by the gus A gene. For observations on sections of roots, samples exhibiting blue-staining GUS activity were fixed in glutaraldeyde, dehydrated with ethanol and embedded in LR White acrylic resin. Sections of 1 μm were cut and counterstained with safranin (0.01% w/v) for light microscopy. Following inoculation of maize, wheat and rice, G. diazotrophicus was detected microscopically intracellularly within the cytoplasm of the cells of the root tips of all these inoculated non-legume crops at 7 days post inoculation. A schematic representation of the interaction is shown in Figure 2. In maize, for example, dark blue stained G. diazotrophicus was clearly visible within the cytoplasm of meristematic cells of the elongating region of the root, and also within their cell walls (Figure 3) (Cocking et al., 2006). Electron microscopy of ultrathin sections of the same roots confirmed that the G. diazotrophicus bacteria appeared to be within membrane-bound vesicles in the cytoplasm. Similar results using inoculation with nifH promoter-GUS-labelled G. diazotrophicus showed blue-stained G. diazotrophicus within the cytoplasm of root cells indicating that intracellular conditions were suitable for the expression of nitrogenase, the bacteria enzyme complex that forms ammonia from gaseous nitrogen (N2) and hydrogen.

The fact that G. diazotrophicus is able to become established in symbiosome-like compartments in the meristematic root cells of cereals and other non-legume crop (Figure 2) indicates that there is likely to be no need for nodulation to achieve symbiotic nitrogen fixation. If stably transmitted from cell to cell fixing nitrogen, these symbiosome-like membrane-bound compartments containing G. diazotrophicus could become diazoplasts, a new type of organelle.

Conclusion – Fulfilling the Vision of Norman Borlaug

We are investigating by nitrogen balances and ^{15}N methodology whether this non-nodular intracellular colonization of cereals by *G. diazotrophicus* results in symbiotic nitrogen fixation of benefit to plant growth. Field trials will need to be performed under a range of environmental and soil conditions to establish reductions possible in synthetic nitrogen fertilizer, while maintaining or increasing yields. There is an ever increasing urgency

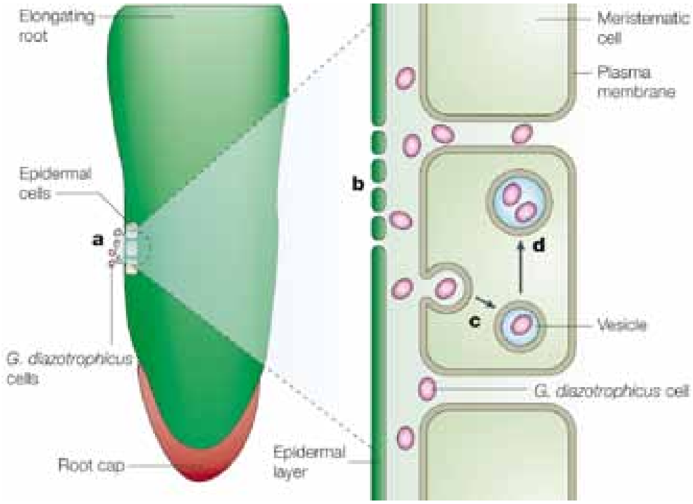

Figure 2. Schematic representation of the interaction of *Gluconacetobacter diazotrophicus* with cereal roots: (a) meristematic zone of elongating root (b) *G. diazotrophicus* penetrates the epidermal cell wall by secretion of cellulase enzymes (c) the plasma membrane pinched off via endocytosis forms a membrane surrounding vesicles containing *G. diazotrophicus* (d) vesicles with *G. diazotrophicus* (diazoplasts) are surrounded by a membrane analogous to the symbiosome membrane of rhizobia (from Cocking, 2009).

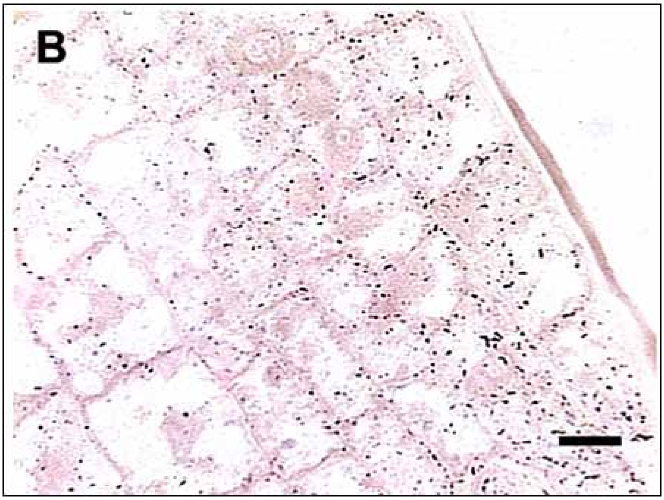

Figure 3. Light micrograph of maize inoculated with *Gluconacetobacter diazotrophicus*: section of region of root tip showing blue-staining *Gus* A-G. diazotrophicus bacteria within cells and in cells walls (scale bar=10μm) (Cocking et al., 2006).

to do so not only to mitigate increases in reactive nitrogen depositions but also for Global Food Security. The Royal Society Report (2009) on Reaping the Benefits: Science and the Sustainable Intensification of Global Agriculture has highlighted the need for research on high-return topics such as nitrogen fixation in cereals to provide the dramatic, but sustainable, improvements in crop production that are urgently required. Food Security and the challenge of feeding 9 billion people requires a multifaceted and linked global strategy including how to optimise the use of nitrogen to not only produce enough food to meet the demand from population increase and the expansion of biofuel production, but also to minimise the impacts of synthetic nitrogen fertilizers on the environment and human health (Godfray et al., 2010).

Norman Borlaug has espoused the idea that perhaps Nature hopes to acquire new sets of abilities, such as action by design, and that maybe Nature needs us (Borlaug, 2002). By interacting cereals with N_2-fixing *G. diazotrophicus* to facilitate intracellular colonization we may be giving Nature the needed helping hand to establish cereal symbiotic N_2-fixation.

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Bt Brinjal: The Challenge of Deregulation

Frank Shotkoski

Introduction

The Agricultural Biotechnology Support Project (ABSPII), a Cornell University-led and USAID-funded consortium of public and private sector institutions, provides 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 engineered crops that otherwise would not be developed. When possible, ABSPII creates public-private partnerships to help leverage both public and private funding sources to help absorb development costs and provide broader distribution channels. ABSPII currently is working in India, Bangladesh, the Philippines and Uganda to develop products with the intention of reducing poverty and alleviating hunger. Descriptions of each of these projects are available on the ABSPII website (www.absp2.cornell.edu/projects/). This paper focuses on the challenges to commercialization of Fruit and Shoot Borer resistant eggplant in India.

Agricultural Biotechnology in Developing Countries

In many developed countries, genetically engineered crops already contribute greatly to agricultural productivity and sustainability. Over the last few years, the largest growth in the adoption of genetically engineered crops has been in developing countries and this trend is expected to continue (James 2007). Multi-national life sciences companies have been leading the way, but they focus primarily on a few crop/trait combinations that have high commercial value and occupy large international markets. Because of the costs and complexity of the issues related to crop biotechnology, many crops and traits of importance to subsistence and resource-poor farmers have been overlooked.

Even when capacity exists in a developing country to undertake biotechnology research, the developers face major challenges to ultimate commercialization. Challenges include lack of political will, unformulated or restrictive regulatory and biosafety policies, a poor understanding of intellectual property rights and licensing and insufficient resources for communication. To address these challenges, ABSPII takes a product-driven approach to build capacity in every step of product development and regulation. By working through the process with an actual crop, all players in the product development and regulation process gain hands-on and real-time experience.

ABSPII's Demand Driven Strategy

ABSPII is designed to complement national and regional efforts to develop and commercialize safe and effective genetically engineered 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 early on with local stakeholders to assure buy-in for the proposed projects and to avoid investment in technology that is unlikely to be adopted. The priority-setting exercise is backstopped by economic studies performed by recognized experts in research evaluation and socio-economic analysis. 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 facilitates 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 testing and eventual commercialization of the product.

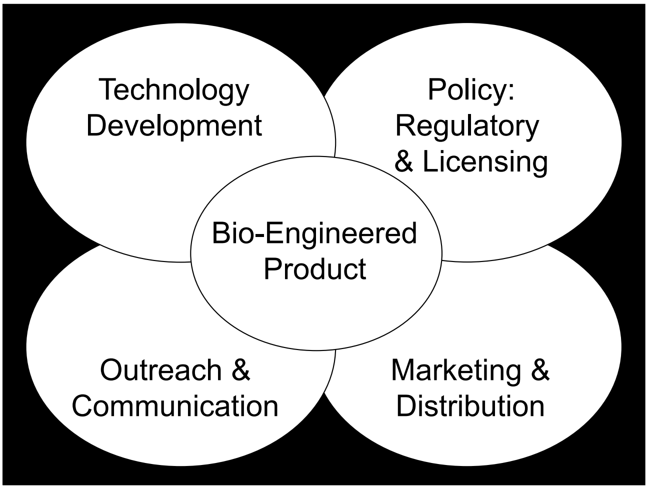

Figure 1. Main elements of an integrated product-driven research-development-delivery for genetically engineered crops. Source: ABSPII

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 all elements of the research, development and commercialization processes. The main elements of each PCP are illustrated in (Figure 1) and include: (i) technology development; (ii) policy-related issues such as licensing the intellectual and technical properties associated with the product as well as applying for and obtaining regulatory approval by the relevant national authorities; (iii) communicating public information to producers and consumers about the benefits, risks and correct management of these new products; and (iv) establishing, or verifying, the existence of marketing and distribution mechanisms to provide farmers access to planting material (Gregory et al 2008).

The specific activities that occur within each quadrant depend on the nature of the particular genetically engineered crop being addressed. For some products, technology development might be the primary focus. For others, product development work might be complete—for example it might be possible for public or private sector institutions to donate the technology to the public good—and issues related to policy, communication and outreach and/or marketing and delivery mechanisms may be of primary concern. In countries where genetically engineered crops are already approved and experience exists, 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-engineered crops, strengthening product development expertise and sourcing existing products for field trials tend to be more important.

Capacity Building and Other Strategy Elements

ABSPII focuses its efforts on building capacity in areas more associated with product development, commercialization, marketing and distribution of genetically engineered crops. Since these activities are broad in nature and complex, it is also necessary to put considerable effort into building capacity in the areas of policy development, regulation, biosafety, 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.

Since many of the ABSPII projects are in the product development phase, it is necessary to acquire governmental approval for field trials to test the technologies under natural conditions. ABSPII has been successful in building capacity in several critical areas necessary to gain field trial approvals. These include facilitating dialogue among those responsible for setting national biosafety standards and promoting policy linkages in relevant sectors impacted 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 (PBS), to work through most policy-related issues.

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

A responsible marketing and distribution system needs to be in place or be planned early in the project. ABSPII has adopted a policy to establish early involvement of downstream partners, particularly private sector suppliers of seed and other agricultural inputs. The seed distributors, private or public, understand that they need to possess the capacity to provide for product stewardship policies associated with the product to maximize the benefits and minimize any risk from using the genetically engineered product.

Bt Eggplant for South and Southeast Asia

Of all the ABSPII-supported products, the fruit and shoot borer resistant eggplant (known as *Bt* brinjal in India) is the closest to commercialization. In South and Southeast Asia, eggplant is an economically and nutritionally important crop and is a staple of human consumption. Its cultivation helps to generate valuable income for farmers and laborers. However, the production of marketable eggplant is seriously compromised due to numerous pest species that feed on eggplant, especially the eggplant fruit and shoot borer (EFSB) *Leucinodes orbonalis* Guenée. The larvae bore inside the terminal shoots, resulting in withering of the plant. The pest also bores into the fruit thus making the fruit unmarketable. Infestation can inflict about 70% crop loss and fruit damage as high as 90% (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 widespread misuse of pesticides causing a multitude of consequences including increased cost of production as well as overexposure to pesticide residue for farmers and consumers. The excessive use of chemical pesticides kills 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 the reduction of the use of chemical pesticides thereby reducing production costs and minimizing environmental risks.

With this background, 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, biosafety and potential economic, health and environmental benefits but also because of the absence of road blocks due to intellectual property rights, favorable prospects for regulatory approval, a high degree of expressed interest from strong local partnership organizations, and the high likelihood of gaining public acceptance for the product due to positive socioeconomic implications (Kolady 2006).

Public-Private Partnership

ABSPII, in cooperation with Hyderabad-based Sathguru Management Consultants Pvt. Ltd. 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 provide resource-constrained farmers access to high-quality open-pollinated (OP) genetically engineered seeds at the relatively low cost of seed production and distribution. Since the market segments catered to by the private and public sectors are different, there are no commercial conflicts arising out of this partnership. Two streams of product development, one under private sector and the other under public sector allows for higher product acceptability and address the critical issue of social equity in the commercialization process. The participating organizations also greatly reduce product development costs (by limiting duplication of work) and share the costs of producing data for the regulatory dossier.

In India, public institutional partners include the Indian Institute of Vegetables Research (IIVR), Tamil Nadu Agricultural University (TNAU) and the University of Agricultural Sciences (UAS, Dharwad).

South-South Partnership

Mahyco has also shared this technology with public partners in Bangladesh and the Philippines. Again, partners realize significant savings by sharing regulatory dossier data and the public-sector organizations are able to develop locally-relevant transgenic varieties for their farmers.

The importance of partnerships is also invaluable for capacity building. Scientists from Bangladesh and the Philippines have participated in study visits India to exchange knowledge, share resources, learn new laboratory techniques and benefit from India's experience with eggplant field trials.

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 LAL TEER Seeds Limited, a multinational vegetable seed producer with a strong market position in the Asian vegetable seed markets. All of the institutions and private enterprises that work with ABSPII on this project were selected because they have capability, infrastructure and a strong track record for responsible seed development and multiplication for distribution to end-users.

In the Philippines, most farmers purchase and cultivate hybrid eggplant. The University of the Philippines at Los Banos (UPLB) is engaged in delivering hybrid seeds to resource constrained farmers. Through its seed production unit, UPLB's Institute for Plant Breeding (IPB) or its constituent body will directly deliver hybrid seeds to resource-constrained farmers. Appropriate licensing agreements will be negotiated with the commercial seed producers who may participate in the distribution of the *Bt* eggplant product.

ABSPII has promoted further collaboration among the three participating countries in the areas 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 exchange and use of relevant regulatory data which addresses local needs. This approach is now being promoted by ABSPII in all its other PCP's.

Regulatory Approval

In all three countries, the public institutions have conducted field trials to assess the efficacy of the technology against the EFSB and to generate biosafety data necessary to develop a regulatory dossier. The field trial approval process is different for each country, but legislation and/or policies exist for each that allow for the trials to be conducted. ABSPII makes field trial applications and conducts the field trials based on the recommendations set forth by the respective national regulatory system. India, as the primary recipient and developer of the *Bt* eggplant technology, was the first generate and submit biosafety and food safety data to its regulatory authority. More than 1000 pages of regulatory data generated by Mahyco in India were submitted to the Genetic Engineering Approval Committee (GEAC) and is available to the public on the World Wide Web (MoEF 2008).

On October 14, 2009, India's GEAC approved the use of *Bt* technology in eggplant. This decision should have allowed for the commercialization of Mahyco's hybrid varieties and allowed the universities to apply for approval for each of the varieties they have developed. This would make eggplant the second GM crop to be commercialized in India and it would be India's first GM food crop. This would also be the first time a GM eggplant had ever been introduced. Anti-GM groups, however, succeeded in applying pressure in the months leading up to the GEAC decision through public protest and an email campaign directed at the Minister for the Environment, Jairam Ramesh.

Ramesh announced he would make a final decision in early 2010, after consultations with agricultural experts, farmers' organizations and consumer groups in January and February. Several consultations were held throughout the country but the last few were cancelled because of an unproductive atmosphere among participants. On February 9, Ramesh delivered his decision to place an indefinite moratorium on *Bt* eggplant pending further safety tests. The main concerns cited in his report were potential risks to long term human exposure and loss of biodiversity.

India's Prime Minister intervened in late February to bridge the differences between the Minister of Science and Technology and the Mister of Agriculture, who supported the commercialization of *Bt* eggplant, and the Minister of Environment. There was a fear that recent events would serve as a disincentive to further investment in biotech research and development in India. The Prime Minister re-affirmed his government's commitment to exploring ways in which biotechnology might help food security and the priority placed on developing indigenous capacity for biotechnology research and development. At the time of this writing, it is still unclear by what mechanism the fruit and shoot borer resistant eggplant will be made available to farmers in India.

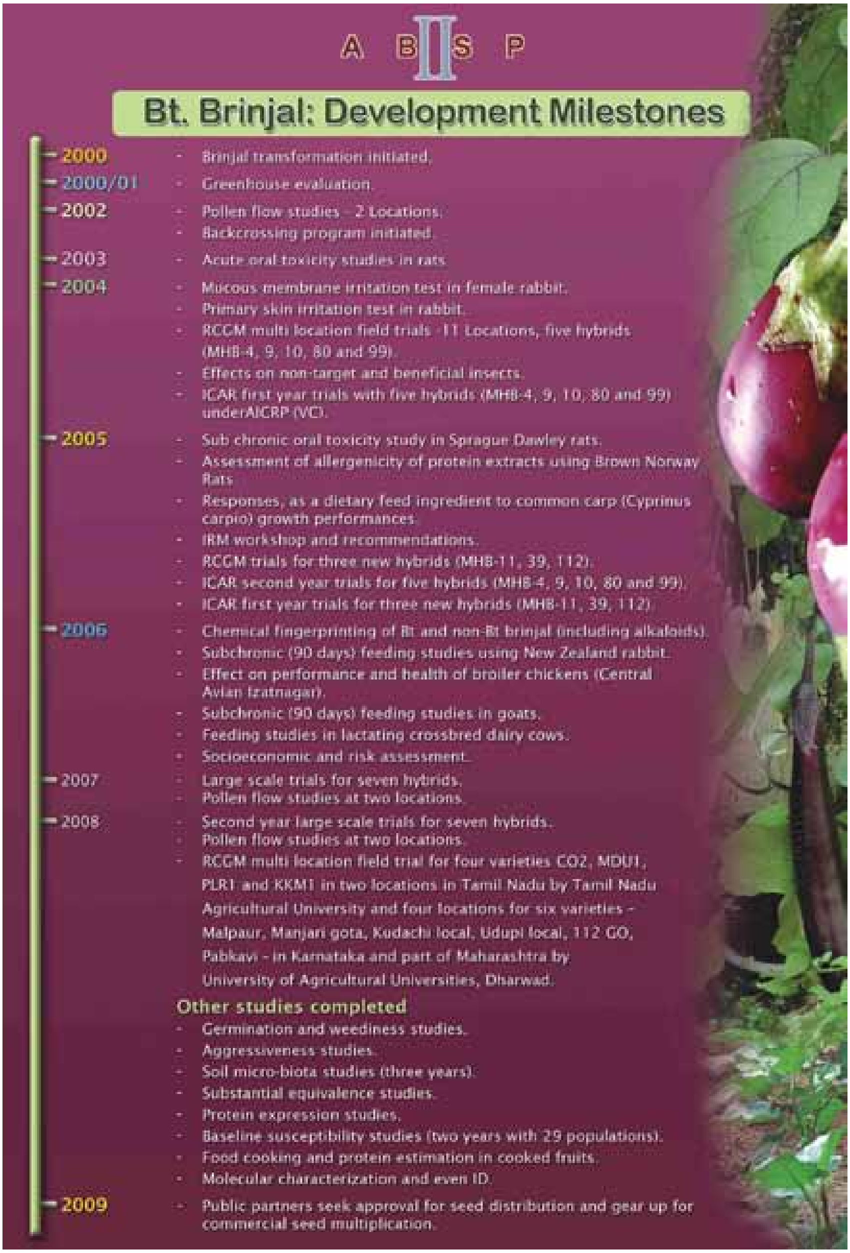

Figure 2. Development Milestones for *Bt* Brinjal in India. Source: ABSPII South Asia Regional Office.

Concluding Remarks

Farmers in the US, Canada and elsewhere have made effective use of biotechnology for over 15 years. Evidence shows that biotechnology has a place in a broad agricultural strategy and ABSPII advocates its use only when conventional solutions are unable to meet challenges to production. ABSPII helps develop the capacity of agricultural universities to provide the high quality scientific research and product development. However, decisions about how to regulate and whether to commercialize such crops are up to each country's elected political leaders.

The *Bt* eggplant project demonstrates that public and private organizations can work together to develop biotechnology that meets the needs of different stakeholders, and make the benefits of biotechnology accessible to resource-poor farmers. The progress being made has not come without challenges. The strategy employed by ABSPII has been quite successful and might be considered by others as a framework, or at least a starting point, for building developing countries' capacity to safely and effectively develop and utilize genetically engineered crops, especially for those crops that are of little business interest to large multinational biotechnology and seed companies. A key lesson learned from the ABSPII experience in India is that there must be more public sector investment in communication to ensure that both policy makers and the public understand the potential risks and benefits of biotechnology.

Further details about ABSPII and its projects are available at www.absp2.cornell.edu.

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Biotechnology, Farmers and Environment in India

Mittur N. Jagadish, Mahesh V., and Villoo Morawala-Patell

We all need to be committed to further facilitate a change in the rural side of the world by enabling a better quality living for the farmers in all countries especially amongst the developing nations. Farmers' community has to be the most admired one anywhere as they are the ones who feed us, feed the animals we depend on, cloth us and they are even sought after to grow crops that can potentially fuel the world. Relatively unexposed to the ever fast changing urban lifestyle, farmers and in particular the tribal farmers maintain the rich heritage, crop germplasm, know-how and they really make serious attempts to conserve the environment or at least do not necessarily contribute to the destruction of it. Yet a significant portion of the urban population is unaware of the farmers' lifestyle let alone the serious difficulties many of them are facing. It is simply reflected by the fact that almost every one of us in the cities never return home from a farm produce market without bargaining to pinch even a very small change for our pockets. While we are ready to pay a very high price for medicines in a pharmacist's shop without whispering even a small word of objection. This is very much the truth in India. The world population is increasing in a very aggressive and arrogant manner aiming to reach 9 billion by 2050. The majority of such an increase is happening in the developing continents such as Africa and Asia. There needs to abundant food, feed, fibre and fuel for all. In this article the focus is on India, its population growth, challenges thereby, the measures we need to undertake to successfully meet these challenges and the overall effect on economy of India.

Similar to the situation in many countries in the Middle East and Africa, the population in India is growing at a rapid rate with the growth projection of 1.15 b today to 1.5 b in 2050. With decrease in cultivable land, water and labour for agriculture and simultaneous increase in expanding urban population, encroaching real estate, destruction of environment and almost violent competition for resources, the challenges are plenty. This is further magnified by the biggest disruption of all- the climate change which again is predominantly caused by human disrespect to nature and our rich inheritance. Agriculture is one of the major contributors to the emission of green house gases. New or modified technological and behavioural solutions are essential if we are serious in our attempts to mitigate the challenges and improve quality of life for all. Innovation must continue to happen in all areas to generate new solutions. Once proven to show that the benefits outweigh risks, extension of such new solutions to all parts of the country and the world where applicable must be made without intervention from individuals who may not be in full synchrony with the rural realities but oppose new technologies without much substantiation.

The Indian economy relies on contributions from several sectors, with Agriculture, Manufacturing and Services as the major players. While the latter two sectors have been making impressive contributions in the recent years, it is the former sector that was the major player for a very long time seeing India through tough times. However even today by and large, agriculture in India engages nearly three quarters of the human population, a large number of farm animals and natural resources and occupying over 40% of the geographical area. Despite the heavy engagement of such rich resources, the contributions to the Indian economy indicate only about 18% by agriculture. In some years, poor monsoons and other climate changes have further decreased the contribution in a predominant manner. In contrast the industry and service sectors boast 29% and 48% respectively and they continue to show positive growth. Experts have suggested that, for India to achieve 8% or more of consistent national economic growth, the agriculture sector needs to gear up from the current growth rate of about 1% to reach 4% and above. Following the food crisis in the 60s at a time the human population was less than 500 million, the regular use of new technologies associated with the Green Revolution have saved millions of lives and have also transformed India from a food importing country to a self-sufficient exporting nation. Since then, the population of humans and animals has grown several folds putting an intense amount of pressure on the country to attain and sustain self-sufficiency let alone continuation of exports. The increased use of land mass for agriculture, indiscriminate use of chemicals and expanding human habitation has decreased wilderness causing deterioration of the environment. New technologies that are environmentally sustainable are essential for India to achieve the second level of self-sufficiency in order to feed and clothe close to 1.5 billion people by 2050, and also to feed a massive number of dependent animals. International studies suggest about 29 billion dollars need to be invested every year in India and China in various sectors such as infrastructure (power, water, roads and transportation), mechanization, storage & marketing and science & technology to meet the demands of the two countries containing largest populations. China appears to be way ahead in all these sectors and India needs to surge forward to survive and to be competitively placed in the global economic scenario.

Crop yield that is operationally enhanced and/or intrinsically devised needs to go up if India were to grow more with less land and other diminishing resources and still be in a position to feed and clothe its people. Operationally enhanced yield refers to effectively controlling many yield-affecting factors such as the germplasm (variety/hybrid) quality, pests such as insects, weeds, fungal/bacterial/viral diseases, water and salinity. The soil make-up and inadequate availability of the essential nutrients are also significant factors that affect crop yield. Intrinsic yield on the other hand refers to how a crop can be made to yield more assuming all other factors are ideal for plant growth. Efficient agronomic practices and good understanding of biochemistry and physiology must be realized in order to tweak pathways responsible for gaining intrinsic yield increase. Circumvention of stress factors that affect yield can happen by measures such as insect resistance management, rotation of crops, breeding stress tolerant traits from wild type relatives to crop hybrids coupled with good agronomic practices. Likewise, development of Aerobic Rice via marker assisted breeding by scientists at the University of Agricultural Sciences has shown enormous potential for growing rice with minimal amount of water. Where there are limitations, such as lack of availability of wild type with desirable traits, new technologies must be ascertained.

Biotechnology of the recent times in combination with the traditional agricultural technologies to increase yields without increasing resources coupled with efficient coordination of R&D across the nation offer an enormous potential. A successful example has been the contribution from

BT Cotton technology which is in practice since 2002. In 2008 Cotton production in India went up by 31%, pesticide usage went down by 37% resulting in an average profit of Rs. 4000 per acre for farmers (ISAAA). Seven to eight years on, the country has doubled its production volumes becoming the second largest cotton producing nation surpassing USA. Crops such as cereals (Maize, Sorghum and Rice), vegetables (Brinjal, Cabbage, Cauliflower and Tomato), Legumes such as Groundnut are in the pipeline awaiting approvals for undergoing trials or for cultivation. Plant Biotechnology also referred to as Transgenic Technology generally involves transfer of a beneficial gene from another organism to the crop of interest followed by several years of development, performance assessment and safety to the environment. Utilizing natural resources without causing any extinction to solve challenges posed in agriculture such as pest and disease attack, labour unavailability, drought, salinity, fertilizer utilization and so on is quite appropriate as there are plenty of beneficial genes in nature. *Bt* Brinjal is case in hand that is awaiting regulatory approval in India. It was put on hold owing to public pressure and since then several petitions have been submitted by proponents of the technology to the regulatory agencies for approval. If introduced, *Bt* Brinjal has the capacity to reduce insecticide usage by 77% making it environmentally friendly, increase in yield by 116% over other hybrids, 166% over open pollinated varieties resulting in a net income of about Rs. 7000 per acre for the farmer (ISAAA). Such potential exists for other crops also. Likewise, labour saving herbicide tolerant technologies are available to help farmers. Herbicide tolerant cotton and corn technologies developed by other companies are in the pipeline for regulatory approvals and when cleared will save an enormous amount of time and hardship in villages. Hand in hand with the introduction and sustained practicing of new methodologies, there needs to be improvement in infrastructure, better access to market, good competitive market practices and most importantly strong urban community support to the farmers. The central and state governments have made available several subsidy schemes for the benefit of farmers and these helpful schemes need to be utilized. An appropriate blend of new technologies and good agricultural practices offer an enormous advantage to India and can make the country a major food basket for the world.

Avesthagen Limited a fast growing company in India appreciates the significant role the farmers perform and the company is committed to developing and providing new and appropriate technologies to enhance their quality of living which in turn will benefit the environment and assist the growth of agriculture sector enabling bigger contribution to the economy of India. In this context, we have developed Environmental Adjusted Crops TM (EAC) technology to provide tolerance to stress factors salinity and drought which are amongst the primary causes of crop losses worldwide. To achieve Environmental stress tolerance, the foremost task was either to prevent or alleviate the damage or to re-establish homeostatic conditions in the new stressful environment thus resuming the normal cellular functions. Changes in gene expression occur in plants following an exposure to different environmental stresses. At Avesthagen the focus has been to identify and isolate beneficial genes using cDNA libraries or differential display from various plants. Many such genes involved in stress tolerance have been isolated and functionally validated in model plants to present the proof of concept. Currently the validated genes are being transformed into the target cereal crops like rice and maize as well as vegetables.

In conclusion, technologies for agriculture need to be primarily farmer focussed who has the challenges of feeding the world. Farmer empowerment is the key to ensuring that rural living is comfortable and acceptable. This will in turn reduce to a large extent the rapid migration of people from the rural side into the city in search for better living.

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Biotechnology, Knowledge and Prosperity in the Mercosur Region

Daniel Pagliano

Summary

The agriculture sector in the Mercosur region is one the most active en terms of adoption of new developments coming from biotechnology-based knowledge. Soybeans, maize and cotton have presented a positive adoption by farmers. The region is nowadays the second concentrated area in a global context.

From the first field trial of a GM crop in the late nineties, the regional agriculture evolved to be very competitive with the participation of a matrix of organizations and companies. Many studies were done in reference to measure the economic impacts of biotechnology. In Argentine, the total benefits of using GM agriculture in ten years from the first trial in 1996 was in the order of 20.4 billions US dollars. In the case of Brazil, who has started later, the benefits to the year 2008 were of 3.6 billions US dollars, and it is forecasted to be of 48 billions US dollars in the next ten years. In Paraguay and Uruguay, with a different dimension, the tendency is similar.

This situation is the result of many actions and decisions. Many aspects were and are contributing to the development of a competitive science-based agriculture. Modernization of the entire system of production, services and logistics components are important. New skills are needed at every level of the system and science and education have proven to be positive driving forces.

Introduction

Comprising the countries of Argentina, Brazil, Paraguay and Uruguay, the Southern Common Market (MERCOSUR) represents a total population of 190 million individuals, living in an area larger than the total surface of the European continent, covering more than 12 million square kilometers. Mercosur or Mercosul (Spanish: Mercado Común del Sur, Portuguese: Mercado Comum do Sul, English: Southern Common Market) is a Regional Trade Agreement (RTA) founded in 1991 by the Treaty of Asunción, which was later amended and updated by the 1994 Treaty of Ouro Preto. Its purpose is to promote free trade and the fluid movement of goods, people, and currency. Venezuela has recently joined the Agreement.

This region is one the most dynamic en-terms of adoption of new developments in agriculture coming from biotechnology-based knowledge.

The adoption of genetically modified (GM) plant varieties is very important, representing nowadays the second concentrated area in a global context (James, 2009).

This situation is not a casual experience. It is the result of many actions, many of them with errors and delays, but today and general speaking; it is possible to observe a very competitive agriculture.

Impacts of biotechnology in Mercosur countries

Soybean is the leading case of adoption of GM plants in Mercosur. Other crops as maize and cotton have followed soybeans and presented also a positive adoption by the farmers.

The harvested area of soybeans has doubled in the period comprising the years 2000 to 2008 (Table 1), representing by the year 2008 the 42% of the global harvested area.

There was an increase in the productivity during this period of time, bringing to the situation that by the year 2008, half of the global soybeans production came from the Mercosur region (Table 2).

The genetically modified crops in Argentina have had an important adoption rate. The first GM soybean was sown as a trial in the year 1996. In the year 2006, after ten years, 14 million hectares were sown with those soybeans, representing an 86% of the total area of this crop (Trigo E. and Cap E., 2006). In that year, others GM crops were sown as 2 million hectares of

Table 1. Evolution of the soybeans harvest area in Mercosur countries (thousands hectares).

Countries	Year								
	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**
Argentina	8.638	10.400	11.405	12.420	14.305	14.032	15.130	15.981	16.380
Brazil	13.640	13.974	16.365	18.525	21.539	22.949	22.047	20.565	21.272
Paraguay	1.176	1.350	1.445	1.474	1.870	1.970	2.200	2.400	2.645
Uruguay	9	12	29	79	247	278	309	367	462
Rest of the world	50.904	51.063	49.717	51.166	53.642	53.277	55.562	50.798	56.112
% Mercosur	32%	34%	37%	39%	41%	42%	42%	44%	42%

Elaborated with data from FAO (http://faostat.fao.org/).

Table 2. Evolution of the soybeans production in Mercosur countries (thousands tons).

Countries	Year								
	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**
Argentina	20.136	26.881	30.000	34.819	31.577	38.290	40.537	47.483	46.232
Brazil	32.735	39.058	42.769	51.919	49.550	51.182	52.465	57.857	59.917
Paraguay	2.980	3.511	3.300	4.205	3.584	3.988	3.800	6.000	6.808
Uruguay	7	28	67	183	377	478	632	780	773
Rest of the world	105.435	108.768	105.544	99.535	120.442	120.354	120.921	107.426	117.223
% Mercosur	35%	39%	42%	48%	41%	44%	45%	51%	49%

Elaborated with data from FAO (http://faostat.fao.org/).

maize (essentially with insects' resistance and being approximately 13% of the total area) and 160 thousand hectares of cotton (105 thousand hectares with herbicides tolerance and 55 thousands hectares with insects' resistance traits).

In the case of herbicide tolerant soybeans in Brazil, the adoption has increased to 70% by the year 2009, when it was in the order of 12% in the year 2003 (James, 2009). It is stated that GM soybean is to increase from the current 13,9 million hectares in the 2008/09 to 25.2 million hectares in the 2018/19 crop seasons (Celeres, 2009).

In the case of Uruguay, by the year 2000 the soybean crop was almost disappeared in the agribusiness scheme. In the year 2008, GM soybeans were the main crop sown in the country totalizing more than 460 thousands hectares (CUS-Seragro, 2008).

The farmers were the sector who received an important part of the total benefits generated and this point may explain the positive evolution of the areas sown and the productions obtained. With the production in place and available, the rest of the sectors were also able to develop their capacities and to contribute to the final business results.

In Argentine, by the 2006 the total benefits of herbicide tolerant soybeans were of 19.7 billions US dollars. The distribution of these benefits were 77.45% to farmers, 3.90% to seed industry, 5.25% to herbicide industry and 13.39% to Government (Trigo E. and Cap E., 2006).

In the case of maize with insect´s resistance, the accumulated total benefit for the period 1998–2005 reaches to the 481.7 million dollars, distributed of the following way: 43.19% for the farmers, 41.14% for the seed suppliers and 15.67% for the Government. Finally, in the case of cotton with insect´s resistance, the considered total benefit for period 1998–2005 is of 20.8 million dollars, with the following distribution: 86.19% for the farmers, 8.94% for the seed suppliers and 4,87% for the Government.

The adoption of genetically modified plants in Brazil represented a total benefit of 3.6 billions US dollars considering the period in between the crop seasons 1996/97 to 2008/09. 78% is explained by soybeans and 18% by maize. A forecast analysis for the next 10 years gave a projection of 48 billions US dollars considering together soybeans, maize and cotton (Abrasem, 2009).

In Uruguay, the Uruguayan Chamber of Seeds have calculated for the period 2004–2008 that the accumulated total benefits were of 1.9 billions US dollars (CUS-Seragro, 2009).

Bio-platforms: clustering resources to be competitive

These figures of continuous growth and adoption of genetically modified crops can be seen as a matrix of coordinated and assumed decisions taken from many components of the agriculture production and commercialization chain.

The uses of a particular plant variety means that many years before a particular harvest and the local breeding programs were working actively in the selection of the most adapted and productive materials. The incorporation of one or more particular genes bringing advantageous traits is also a process which implies time, humans and materials resources and the sum of thousands of small and large actions.

Once a group of prominent materials is available, they must be evaluated in agronomic protocols and in the framework of well established biosafety regulations. This process ends with a short list of potential plant materials that needs to be accepted and adopted by not only the farmers, but for the logistics and commercial operators as well, in order to in total fulfill the market demands.

For these reasons, the increased and positive evolution of biotechnology-derived crops in the Mercosur region must be seen as the result of an entire productive, commercial, regulatory, promoting complex and robust bio-platform.

The issue of to realize the importance of dimensions and times is vital for the success of the platform.

The decision of to develop a competitive breeding program implies long term vision, supported with prospective analysis and science trends evaluations.

A particular farmer decision of to sown in a particular year, depends in many short and medium terms aspects as prices and weather forecasts, availability of resources and at the end, an expectation of a benefit.

The regulatory framework operators, the logistics and the commercial participants in the platform take a mixture of different decisions, either in short or medium time terms.

Competitive biotechnology based agriculture must be seen as the result of a pool of different decisions that coexist and evolutes in coordination and acceptation.

There are some components in the platform which have shown of being very important in the positive evolution seen:

- The revolution seeing in agriculture engineering is a very important component. With the leading case of no tillage practices, there was a modernization of the machinery available for all the different components used in productive and logistics schemes. The change was not only in machinery itself, it was in the way of thinking of many farmers
- The formation of a well established agriculture related services sector is a feature of this positive development. An important number of new companies were created in the last years, offering services for tillage, harvest, animal feeds production, plant health treatments, transports, logistics and other particular services. Many of these companies are small sized and family-structured companies. It is very important to underline the issue that many of them are

ruled by young entrepreneurs, who have found a business opportunity in the countryside region and so deciding not to migrate to big cities

- It is also important that the adoption rate of technologies related with the sustainability of the production capacity, as for example no tillage technologies and good agriculture practices (GAP). These new standards compromises with new attitudes and skills needed 'to be part' in the new bio-agri-culture.
- The financial and commercial related organizations have also evolved with the result of a large availability of tools and business models
- The industry of agriculture technology inputs as inoculants and growth promoters have shown an important development. These types of companies are also contributing to the uses of biotechnologies. In the case of inoculants, analysing the Argentinean soybean campaign 2004–2005 and assuming a protein content in the beans of 40%, the data gave a total of harvested protein of approximately 37.126.400 Metric Tons, or what is just like to say that 6.456.765 Metric Tons of nitrogen or their equivalent in urea: 14.036.446 Metric Tons (González Anta, G. 2006)
- The education and science-based organizations matrix have also contributed with significant new capacities. There are many ongoing programs which cover materials and courses for different ages, communities and social backgrounds (as for example: Redbio.org; porquebiotecnologia.com.ar). Also, new institutions have lead the process of acquiring the necessary knowledge at a farmer level, as it is the case of the Argentine No-till Farmers Association (aapresid.org.ar)
- There are ongoing programs to promote the interaction in the triangle academia, private sector and governmental sector. Networking is promoted either in a country or regional levels. In terms of science development, the excellent Brazilian case of the *Xyllela* genomic project is a good example which triggered excellence and concrete spinoffs (*Nature*, 2010). The more recent regional initiative at the Mercosur level is the project known as 'Biotecsur' This is a platform in the region created to establish a common long-term vision for the development and application of new biotechnologies (biotecsur.org).

Challenges and Opportunities

Integrating efforts from countries to a region are necessary to develop biotechnology in a way that allows maximizing benefits. This is an issue for the Mercosur region as it is for every region where biotechnology in agriculture has the potential of bringing new opportunities.

The integration process must be developed with 'conscience factors', which should lead to incentive desirable attitudes and the perception that any part of the bio-platforms counts in contributing to the entire competitive and sustainability capacities. Some of the 'conscience factors' may include:

Cooperation

Cooperation is a keyword in the new agri-culture. There are many pre-competitive aspects that can be afforded with a wide spectrum of organizations and participants of the bio-platforms. It is important in order to scale up processes and to capture values which are dispersed in many institutions and companies. To reach the market, many parts must build up the value of a particular product. In this regard, the academic sector should be active in offering scientific capacities and in the interaction with the private sector, the innovation will occur more easily. The clusters and consortia formation must be encouraged. Cooperation must be seen in any direction, intra-organizations, intra-country, intraregional and between regions. It is important to enhance both paths: North-South and South-South.

Education is the key

The development of new skills considering scientists, farmers, workers and every operator in the platform must be assumed as a continuous and progressive process. The generation of prosperity may be seen as a desirable objective of the community of technology, production and commercialization. This is something that should be present at any level, from the individuals to the general strategies. Early discover of talent is important. Universities and the entire educational system may be in alert to identify the new generation of scientists and entrepreneurs, in an environment of excellence and promoting new ideas and positive attitudes.

Conclusion

Biotechnology in agriculture has already shown of having a great potential to transform positively the societies. In the Mercosur region, agriculture has been positively transformed with the use of biotechnology-derived plant varieties. The amount of genuine resources which came from the use of GM plants has driven to develop an endogenous and sustainability capacity.

The Mercosur example can be followed in other areas of the world.

The opportunities are there. Biotechnology can valorize knowledge, giving a new dimension of interactions between Academia, private and public sectors.

Societies must realize that talking about biotechnology is more than life sciences. It is about opportunities for social and economic development. It is important to understand the necessity to pass from talking about 'Genetics concepts' to 'Development concepts'.

Acknowledgement

I would like to express my acknowledge to the Bibliotheca Alexandrina for promoting the excellent initiative of BioVisionAlexandria.

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Agricultural Biotechnology in Europe

Ricardo Serra Arias

Summary

European farmers face costly challenges in order to implement sustainable farming. Pest development and weed control are two key issues to address. The use of biotechnology through insect resistance (IR) GM crops in the EU has brought important economic benefits for European farmers. The case of *Bt* corn shows incremental yields that range from 6% to 10% *vs.* conventional varieties. At the end of the 12th year of *Bt* corn commercial plantings in Spain, 88% technology penetration has been reached, representing 22% of the total corn grain surface in this country. Efficient farming is a must to satisfy the local Food-Feed Chain supply and biotechnology is a very useful tool to improve crop yields in a sustainable way, as is the case of the key farming countries worldwide. Within the current very strict and reliable regulatory process in the EU, the approval of new technologies is demanded by farmers in order to improve, in a sustainable manner, their efficiency and competitiveness.

Introduction

European farmers have to face major challenges in their crops like pest and weed control. Pest control is a global concern and it is expensive. Farmers need to look for more efficient and sustainable ways to manage their crops. Biotechnology, through GM crops, offers an opportunity to implement new technologies aiming to such targets.

Paraphrasing Brooks[1]: 'Across the EU the potential adoption area for GM IR [Insect Resistant] maize is in a range of 2.25 million ha to 4 million ha, depending on the annual levels of pest pressure. At these levels of adoption, the annual direct farm income benefit potential (at 2007 prices) falls within a range of €160 million and €247 million'

Costly challenges

European Corn Borer (ECB) is present all over Europe, bollworms dramatically damage cotton crops and diabrotica is a growing threat for corn growers as a result of its fast expansion from Hungary, the former Yugoslavia and Romania. Also, weed control is a must for all farmers in any crop.

Spain is no different, and Spanish farmers are facing this type of challenge too. For instance, ECB is an important and harmful pest in the country, mainly in the Ebro valley area and other regions with important ECB spots (Madrid, Castilla-La Mancha—Albacete, Extremadura or Andalusia—in second crop).

The cost of pest and weed control is high and current treatments are not fully satisfactory. For example, the limited control of ECB with insecticides reaches 35€/ha, the Bollworm control in cotton ranges between 400 and 600 €/ha, and the weed control in corn or cotton means a cost per hectare of 50 €.

Biotechnology benefits

Genetically Modified (GM) crops in Europe are bringing tangible value for farmers. In the case of *Bt* corn (resistant to ECB), data[2] of eight countries (Spain, Portugal, France, Germany, Poland, Czech Republic, Slovakia and Romania), from 512 data points, showed a yield advantage of 800 kg/ha in favour of *Bt* corn *vs.* conventional one, representing a 7% increase (12,100 kg/ha *vs.* 11,300 kg/ha).

1. Brookes Brookes, "The Existing and Potential Impact of using GM Insect Resistant (GM IR) Maize in the European Union", **PG Economics**, http://www.pgeconomics.co.uk/pdf/btmaizeeuropejune2009.pdf

2. Source: Monsanto TD department.

These data are consistent with those ones reported by Brooks (PG Economics Ltd.) who indicates an average yield of GM Insect Resistant (IR) maize relative to conventional of +6.3 (1998–2003) and +10% (2004 onwards).

As a consequence of that, farmers are improving their profits, as it is reflected in their Gross Margin (GM) increase. For example in the Saragossa area, between 2002 and 2004, this growth ranged between 105.77 €/ha and 135.08 €/ha.[3]

Bt corn was introduced in Spain in 1998 and currently is a normalized crop[44] representing 22% of the corn grain surface in Spain. Taking into consideration that the ECB affected area is only a 25% of the total corn surface (around 100,000 ha out of a total corn surface of 400,000 ha), it represents a technology penetration of 88%.

The Spanish experience shows that biotechnology is adopted by farmers where is needed. Farmers from important corn areas, but without ECB pressure, do not plant *Bt* corn, i.e.: Castilla y León or Galicia.

Farmers need the access to additional technologies to deliver their role of being sustainable ones.

Biotechnology contributes to a more sustainable farming from the triple perspective: Economic, Environmental and Social.

Additional technologies, to the currently implemented one in Spain (*Bt* corn), contribute to maintain the farmer profitability and competitiveness, at the same time that reducing the environmental footprint–through a lower use of pesticides or thanks to facilitate the implementation of low footprint farming models like Conservation Tillage, helping to reduce the Greenhouse Gases (GHG) emissions. These technologies contribute to maintain the farming activity and, as a result of that, to secure the Rural Development.

Efficient farming is a must to satisfy the local Food-Feed Chain supply, mainly when huge importations are needed. By instance, Spain and Egypt

3. Manuel Gómez-Barbero, Julio Berbel, Emilio Rodríguez-Cerezo, "Adoption and Performance of the First GM Crop Introduced in EU Agriculture: Bt Maize in Spain", **European Commission, Joint Research Centre**, http://ftp.jrc.es/EURdoc/JRC37046.pdf

4. "Semillas y plantas de vivero", **Ministerio de Medio Ambiente y Medio Rural y Marino**, http://www.mapa.es/es/agricultura/pags/semillas/estadisticas.htm

face similar challenges with very big annual demand of imported corn grain, 91 kg/habitant/year in Spain and 59 kg/habitant/year in Egypt.

Such an efficient farming demands the farmer right to choose the type of necessary technologies to implement in their farms. So, key farming countries in the world fit with Biotech ones, USA, Canada, Mexico, Brazil, Argentina, India, China and South Africa, for example.

European Union and Biotechnology

Biotechnology must have a science based approach, and the EU has the most strict regulatory process supported by the independent, and highly respected, European food Safety Authority (EFSA)[5].

The EU approvals delay is not based on scientific assessments but on ideology and particular economic interests of some Member States.

The March 5th, 2010 cultivation approval for the 'Amflora'[6] potato must be a firm change rather than an exception.

Farmers in the world are no different, regardless of the country where they are based, and their needs and features are similar. At the end of the day, farmers are farmers! And, they must have access to the same tools in order to be efficient, competitive and sustainable.

Acknowledgements

To all the European people; farmers, doctors etc who are trying to change the public opinion in order to have a sustainable agriculture, and to Carlos Vicente, from Monsanto, who helped me in my Biovision experience .

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International Efforts in Biodiversity Conservation

Jeffrey A. McNeely

Summary

Threats to the world's biodiversity continue to grow, despite the efforts of the convention on Biological Diversity and other conservation initiatives. Climate change has risen to the top of the list of environmental concerns, but the effects of climate change will be felt by people through changes to ecosystems and biodiversity. A new and more integrated strategy for conservation has been promoted by the Millennium Ecosystem Assessment, based on the concept of ecosystem services. These are the benefits that people receive from ecosystems, in four main categories: supporting services; regulating services; provisioning services; and cultural services. The latter category is especially important in highlighting the key role played by people in conservation, leading to another new approach, known as 'biocultural diversity conservation.' It recognizes that the human dimension in conservation has been ignored for too long, when the only realistic hope for conservation is to ensure that the people who are most directly affected by changes to ecosystems are the ones who must play the key roles in their conservation. Major future challenges to biodiversity conservation are likely to include climate change, demographic shifts, food security, and human health, all of these will require appropriate new policies. For conservation organizations, policies should include: first, do no harm; second, strengthen the capacity to adapt to change; third, seek to integrate the value of ecosystem services into the economy; fourth, use economic instruments to support the conservation of ecosystems; and

fifth, build political will for conservation. Change is inevitable, but making human well-being the focus of change will require new ways of thinking about conservation and converting policy into action.

Introduction

Protected areas have been one of the most successful biodiversity conservation strategies promoted by governments, non-governmental organizations, and indigenous peoples around the world. Nearly 13% of the Earth's land surface is now under legal protection. Demarcating land where the human touch is relatively gentle enables biodiversity to flourish, but only when these areas are effectively managed. While protected areas have existed in various forms for thousands of years and will always help humans live in balance with the rest of nature, they are not sufficient by themselves for mitigating the pace of ecosystem degradation or species extinction. Since the entire world cannot become a protected area, governments, the private sector, conservation organizations, and local people are now working together to build on the eternal link between people and nature in hopes of finding a more sustainable relationship among the various forms of life on Earth.

Many conservation organizations are working together with other partners to apply their institutional capacity in biodiversity conservation as a tool for improving human well-being. They also hope to share complementary skills through partnerships and alliances. These initiatives have been motivated by the fact that healthy ecosystems deliver essential services to all people, but are especially important for the livelihoods of the estimated 900 million rural people still living in poverty. The countries with the lowest per capita gross national product are largely dependent on their natural capital—forests, fisheries, and agriculture—to fuel economic development, making them vulnerable to the various forms of ecosystem degradation. At the local level, poor people depend directly on ecosystems to support their livelihoods, often harvesting nature's produce to earn an income.

In spite of conservation efforts, habitat change, climate change, invasive species, over-exploitation and pollution continue to undermine the capacity of ecosystems to meet human needs (Millennium Ecosystem Assessment, 2005). The consequence is a downward spiral of environmental deterioration as demand for resources increases and supply decreases, leading to deepening poverty and social insecurity.

Many people working in conservation believe strongly that poverty is correlated with declining biological resources and ecosystem capacity. Indeed, Indira Gandhi, at the United Nations Conference on the Human Environment, held in Stockholm in 1972, famously said that 'poverty is the worst form of pollution' (Dwivedi and Vajpayi, 1995). On the other hand, excess consumption undoubtedly causes much more environmental degradation, often removing the rural poor from their land or denying them access to resources they have long considered their own (Fisher, et al., 2005). Nevertheless, biodiversity conservation needs are seldom factored into development assistance actions designed to reduce poverty. (but see Sayer and Campbell, 2004, and Schelhas and Pfeffer, 2008, for some positive examples). All of this suggests that people must be at the center of conservation efforts around the world.

Some Key Factors in a New Approach to Conservation

McNeely and Mainka (2009) drew on a wide range of initiatives presented at the IUCN World Conservation Congress held in Barcelona in 2008 to identify several key factors in promoting international collaboration in conserving biodiversity and supporting human well-being. Some of these are briefly discussed below.

Adapting to change

The Millennium Ecosystem Assessment (2005) found that about 60% of the ecosystems services assessed are degraded. The loss of biodiversity implies fewer options for adapting to changing conditions. Just four plant species—wheat, maize, rice and potato—provide more than half of the plant-based calories in the human diet (Pollan, 2006), yet all are vulnerable to various threats involving ecosystem change. People are less able to depend on degraded ecosystems and must rely on fewer biological resources, thereby increasing their exposure to risks posed by environmental and social changes beyond their control. Social means of adapting to changing conditions can take the forms of improved technology, migration to places offering new opportunities, or changing behavior (for example, becoming a fish farmer rather than capturing wild fish). Maintaining cultural diversity is an essential source of social adaptation (Suzuki and Knudtsonb, 1992) because tapping into inventions and practices from many cultures will better equip people to adapt (Maffi and Woodley, 2010). Therefore, conserving cultural diversity is an essential part of conserving biological diversity; indeed, both forms of diversity are part of the capacity to maintain resilience and adapt to changing conditions (Maffi, 2001). This human capacity to adapt makes it possible for people to be resilient to changing conditions, to reduce their impact on natural systems, and to promote sustainable ways of living.

Recognizing people as part of ecosystems

To conserve biodiversity, land must be protected from people. Or so many conservationists thought. As a result, people were excluded from formal conservation tactics for conserving biodiversity, such as protected areas. But this was misguided. The global human population quadrupled from about 1.4 billion to 6 billion during the 20th century, and continues to grow by about 80 million people per year. Further, global consumption of resources has increased by a factor of 16 over the same time period, putting increasing pressure on the land. As a result, trade-offs need to be made among protected areas, agricultural land (with the new pressure of biofuels), and spreading urbanism. For people who rely on ecosystems for their livelihoods and who maintain sacred natural sites (Verschuuren et al., in press), this squeezing has convinced them that they must demonstrate that people are part of nature. Many of them have shown that indigenous and local communities can indeed contribute to conserving biodiversity, and have been accepted into the mainstream of conservation (Beltran, 2000; Laird, 2002). They have been supported by increasing evidence of the significant overlap between biodiversity and cultural diversity, termed 'biocultural diversity' (Maffi, 2001). This overlap is evident on maps where cultural diversity 'hotspots' (areas of high cultural diversity, as indicated by high linguistic diversity) are shown to overlap quite considerably with biodiversity hotspots (Harmon, 2002). The modern concept of nature among many conservationists now includes people, thus facilitating collaboration with indigenous and local communities.

The people living between protected areas and urban centers are not the only ones building this case. Farmers and agricultural policy analysts are making a similar point as well (McNeely and Scherr, 2001; Takeuchi et al., 2003). Examples from the conservation field include the World

Heritage Convention's designation of cultural landscapes. Increasingly, this perspective is being integrated across many conservation programs (McNeely and Mainka, 2009).

Ecosystems Services: A New Way to Look at Nature

One important advance in promoting international collaboration in the conservation of biodiversity has been the development of the concept of ecosystem services. This concept arose in the 1970s, was given a major boost by Daily (1997), then became part of the mainstream with the publication of the Millennium Ecosystem Assessment (2005). McNeely et al.(2009) have produced a popular version aimed at a broader audience.

Ecosystem services builds on a fairly obvious concept: Ecosystems are essential to human well-being. Ecosystems have provided the functions of nutrient flow, supported the predator-prey interactions that helped drive evolution, and even generated the current atmosphere that supports life on Earth. As humans evolved, they benefited from many of these basic functions, which provided important services. Many cave paintings in Europe and elsewhere; dating from the Upper Paleolithic 30,000 years ago or earlier, depict scenes of hunting large mammals. Thus, wild harvest may be the first documented ecosystem service, though clean water and a supporting atmosphere predate our species. With the emergence of civilization through the establishment of irrigated agriculture, humanity began to realize the benefits of a much broader spectrum of ecosystem services and the hazards of undermining them. For example, the writings of Plato in 400 B.C. implicated deforestation as causing erosion and drying springs (Goldin, 1997). The civilizations of India, East Asia, and Southeast Asia mobilized water and nitrogen-fixing algae to create irrigated rice-growing ecosystems that produced the world's richest cultures of those ancient times (McNeely and Wachtel, 1988).

So what, exactly, are ecosystem services? Simply, they are the benefits that the functions of ecosystems provide to people. The concept of 'ecosystem' highlights the importance of interactions between elements of biodiversity—at a range of scales—and interactions between living species and the non-living environment. No single 'piece' from the system can provide services alone, independent of such interactions. Indeed, it is those interactions that support, regulate, and provide the provisioning and cultural benefits that people derive from biodiversity. As such, people do not derive services from a range of scales of biodiversity independently; rather, they derive services from ecosystems and elements of them functioning as a whole. When the system is degraded, people derive fewer services, providing a powerful justification for the new focus on conserving ecosystems and the services they provide.

People manage ecosystems in order to gain more benefits from them. Ecosystem services can be an empowering term that demonstrates how managers and decision-makers can vary their approaches to managing biodiversity for services that benefit people. The Millennium Ecosystem Assessment (2005) classified ecosystem services into four groups: supporting services; regulating services; provisioning services; and cultural services.

Supporting services are those ecosystem processes necessary for the delivery of all other ecosystem services—and, indeed, life on Earth itself. Arguably the most fundamental of these is primary production, the biochemical process through which living things produce organic compounds from energy and carbon dioxide. Its main pathway is through the capture of energy from the sun by plants, algae, and cyanobacteria through photosynthesis. The other major supporting service is that of nutrient cycling of carbon, nitrogen, phosphorus, and sulfur (and other elements including iron and silicon) between the land, water, and the atmosphere. The presence of these nutrients is essential in maintaining ecosystem productivity, but in excess they can be damaging pollutants that reduce ecosystem productivity and threaten human health.

Regulating services are the benefits that humanity obtains from the natural regulation of ecosystem processes. Enormous investment is focused on the regulation of climate and air quality, given the damage caused by human-driven atmospheric pollution by greenhouse gases (GHGs) from burning fossil fuels, growing crops and livestock, and clearing forests, and of the importance of air quality regulation more generally. Similar waste-processing services are also essential in maintaining the quality of waters and soils through erosion control and detoxification. Intact and functioning ecosystems provide great value in mitigating the effects of catastrophic natural events (e.g., landslides, earthquakes, floods, and tsunamis) and helping people to cope with disasters. Other regulating services derive from the ecological interactions between species. These include pollination (which supports a third of the world's agricultural output), natural limitation and biological control of pest species, and the regulation of waste and human diseases.

Provisioning services are the products obtained directly from nature. Intact habitats are fundamental in maintaining surface fresh water—which represents a mere 0.02% of the world's water overall. Other important provisioning services are provided by direct harvest from ecosystems, including hunting and gathering of a range of species, marine and freshwater fisheries, and the harvest of plants for timber, fuel, and fiber. The same processes are replicated for domesticated species through pastoralism and agriculture. The production of biomass fuel, from firewood and charcoal, from grain ethanol, and from animal dung, could be considered another provisioning service. Nature also provides the basis for health and bio-tech industries through medicine, and genetic resources.

Cultural services are the non-material benefits that humanity derives from biodiversity, including educational, recreational, and ecotourism benefits as well as aesthetic and scientific ones, cultural identity with ecosystems, and spiritual and religious values . The measurement of many of these cultural services is challenging, but ultimately these values may provide some of the strongest rationales for the conservation of nature and, indeed, for human well-being overall.

These categories of ecosystem services often overlap. For example, the supporting service of nutrient cycling also contributes to the regulating service of climate maintenance—with their differentiation being primarily one of time scale. Water appears in many of the services and is recognized by the MA as its own service no less than four times, including water cycling as a supporting service, water flow regulation and water purification and waste treatment as regulating services, and fresh water as a provisioning service.

Valuation of Ecosystem Services

The variety and importance of services that people derive from nature are clear from even this brief survey. , But far more needs to be done to quantify the benefits of ecosystem services. To help fill this gap, a study on The Economics of Ecosystems and Biodiversity (TEEB) was launched in 2007 in response to a proposal by the G8+5 Environment Ministers, meeting in Potsdam, Germany. This is an independent study hosted by the United Nations Environment Programme and drawing together the experience, knowledge and expertise from all parts of the world in the fields of science, economics, and policy. It is designed to guide practical policy responses to the growing evidence of the negative impacts of continuing losses of biodiversity and ecosystem services. It has already launched several reports (TEEB, 2009), with the final report due in October 2010 at the Conference of Parties of the Convention on Biological Diversity (to be held in Nagoya, Japan).

Many ecosystem services are public goods that flow from source ecosystems to human beneficiaries over very large geographic scales (e.g., nutrient cycling operates at the global scale as well as at very local scales). Others, such as climate regulation, are also delivered over very long time scales. Even local-scale ecosystem services are often very hard to measure and monitor. Perhaps most significant, the costs of maintaining ecosystem services are often incurred by different people than those who enjoy their benefits, as in the case of upland communities maintaining forests that regulate the quality and quantity of water used mainly for downstream agriculture and industry.

Ecosystem services are only valuable in economic terms where people derive benefits from them. Thus, for instance, while the biophysical process of water production and flow in the boreal region of the far north is considerable, relatively few people derive benefits from it (because of the region's low population density), so its economic value is modest. However, the climate-regulation values of this region are substantial.

An even bigger problem is that the benefits-transfer approach fails to address equity. It assumes that all people benefit equally from the provisioning of ecosystem services, whereas in fact it is not the absolute contribution but rather the relative value of an ecosystem service to human life that is the variable of greatest interest to the people most directly affected. For example, conservation of a forest watershed may deliver great absolute economic benefit to a large city in a wealthy country relative to the alternative costs of water treatment and processing. But if considered relative to its contribution to human livelihoods, equivalent forest conservation in a poor, dry country might have far greater value.

Ecosystem services are a conservation tool that helps make the business case for conservation, but perhaps more important, also places human well-being at the centre of nature's capital. Some conservationists might not agree with the assumption that the central driver of ecosystem services is the premise that ecosystem degradation is a result of an imbalance in the market forces between human economy and nature's economy. But economists argue that by placing fair value on ecosystem services, the market will adequately reflect the relationship between human beings and ecosystems, and consequently serve as a tool for the conservation of nature. Ecosystem services and the schemes that develop from the concept are meant to complement other kinds of conservation work, provide strategies for conservation, and link natural capital to human capital.

Growing understanding of the importance and value of ecosystem services over the past thirty years has stimulated a series of key events and, emerging from these, important policy initiatives aimed at fostering international collaboration in conservation. The most notable of these was the United Nations Conference on Environment and Development, known as the Earth Summit, held in Rio de Janeiro, Brazil, in June 1992. One major outcome of the Earth Summit was the development of the United Nations Framework Convention on Climate Change (UNFCCC) to which 192 of the world's countries are now parties.

The other significant result of the Earth Summit was the signing of the Convention on Biological Diversity (CBD). A total of 191 nations are now party to the CBD. The objectives of the convention are the conservation of biodiversity, the sustainable use of its components, and the fair and equitable sharing of the benefits arising from the use of genetic resources. The notion of ecosystem services is therefore deeply embedded in the CBD through the concepts of 'sustainable use' and 'benefits.'

Conclusion

Policy changes have made possible partnerships between local people and conservation organizations, and for local communities to take the lead on conservation projects. These increasing opportunities will have new challenges ahead as conservation focuses on climate change, the ecological effects of an increasingly urban human population, food security and health.

While people living in mountains, polar regions, and coastal areas may be especially vulnerable to **Climate Change**, indigenous peoples and local communities in drylands like the Sahel and the Middle East will also be affected. Desertification few technical solutions, which means that people may need to migrate in order to adapt. Peoples living in the Arctic will need to make some significant adaptations as ice sheets recede, permafrost melts and fish stocks change. Mountain people will need to adapt to receding glaciers and the resulting loss of water during the summer season (which often have been the primary growing season for crops or high-altitude grazing. For coastal and island-dwelling people, rising sea levels may force moving to higher ground, or abandoning their island altogether. Some transformations may be beneficial, but adaptation is more likely to be traumatic as some species of plants and animals wildlife disappear, forcing many cultural practices to adapt as well.

Demographic shifts will continue as populations continue to grow and, according to most projects, consume more resources. Today, over half the population lives in urban areas, becoming more distant from the ecosystems upon which they ultimately depend.. This trend is likely to persist as people continue to migrate to cities in the search of better lives. When people return to the land in times of financial crisis, some may find the bucolic life more amiable, but others will return. Governments may also prefer urban populations because it is easier to deliver services, to people living closer together, for economies of scale. People living in cities can benefit from a wider variety of jobs, better access to markets, and improved services medical care and education. Migration to cities has nurtured economic growth, but in the future cities may attract 'environmental refugees' fleeing the negative impacts of pollution and climate change.

Food security is an issue which will become more and more pressing as the global population continues to grow; FAO, for example, predicts that farmers will need to produce 50 percent more food by the year 2050. Reducing hunger is more a political and economic problem than an agronomic one (Pollan,2006) and therefore is often more influenced by market forces than demographics. But as food prices increase and research leads to more intensive application of technology to farming, the politics of food will become more complex. Biodiversity and especially the provision and maintenance of genetic diversity will grow in importance, and the agriculture-related ecosystem services (especially related to provision of water) will demonstrate their importance (MA, 2005). Perhaps new forms of agriculture will be developed that are more biodiversity-friendly, such as ecoagriculture (McNeely and Scherr, 2003; Takeuchi, 2003)...'

Human health and emerging infectious diseases are likely to become an even more important part of globalization, as human populations become more mobile, climate change encourages new distributions of disease vectors such as mosquitoes, and invasive species spread new diseases (Aguirre et al., 2002).. Ecosystem changes can have significant implications for diseases, as shown by SARS, avian influenza, West Nile virus, and malaria.. Such diseases will continue to spread as climate change disrupts living patterns. Disease will be a major challenge for people for years to come. An exploration of traditional medicines and medicinal plants is an arena for work with indigenous peoples on the intersection of biodiversity and health.

The world needs to invest in a new system, one that does not give perverse incentives for unsustainable growth. The world needs a system that shifts people's consumption habits, one that invests in green infrastructure and one that thinks strategically about how we are to live on this fragile planet. All the world's collapsing systems make it painfully clear; it is time for a change.

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The World Library of Toxicology, Chemical Safety, and Environmental Health (WLT)*

Phillipe Wexler

Abstract

The World Library of Toxicology, Chemical Safety, and Environmental Health, commonly referred to as the World Library of Toxicology (WLT), is a multi-lingual online portal of links to key global resources, representing a host of individual countries and multi-lateral organizations. The Site is designed as a network of, and gateway to, toxicological information and activities from around the world. It is built on a Wiki platform by a roster of Country Correspondents, with the aim of efficiently exchanging information and stimulating collaboration among colleagues, and building capacity, with the ultimate objective of serving as a tool to help improve global public health. The WLT was publicly launched on September 7, 2009 at the Seventh Congress of Toxicology in Developing Countries (CTDC-VII) in Sun City, South Africa.

Introduction and Genesis

While a handful of Western countries tend to dominate the world in the generation of toxicology research, data, and activities, virtually every

* First published in **Human and Experimental Toxicology** on November 11, 2010.

country makes some contribution to the output of this information. Certain countries have robust toxicology infrastructures and a well identified information frameworks, while others do not. While countries have traditionally been relatively provincial in focusing on their own activities, the era of globalization has made it clear that such an approach requires serious reconsideration, and that toxicology from all quarters needs to be better inter-connected.

The importance of environmental information exchange has been raised as far back as the seminal 1972 Stockholm Conference on the Human Environment. The 1992 UN Conference on Environment and Development (aka Earth Summit)1 held in Rio de Janeiro, Brazil, called for "intensified information exchange" in Chapter 19 of its Agenda 21. As a result, a Global Information Network on Chemicals (GINC) was proposed, in 1994. GINC was placed under the framework of the Inter-Organization for the Sound Management of Chemicals (IOMC), with a pilot phase in Asia, and the support of the Japan Ministry of Health, in 1995. A series of meetings were held through 2000, and the GINC was gradually developed on the Web.

Financial considerations forced maintenance to be suspended in 2003. Shortly thereafter, the US National Library of Medicine (NLM), the world's largest biomedical library, and a component of the National Institutes of Health, after consultation with several of the GINC's key developers, decided to take up the mantle and create a similar, but more broadly based portal linking toxicology information from around the world. Under development for several years but accessible only as a password protected pilot site, the WLT was ported to INND/Toxipedia (http://www.toxipedia.org) in 2008, with funding from NLM, and in partnership with the International Union of Toxicology (IUTOX). It was publicly launched on September 7, 2009 at the Seventh Congress of Toxicology in Developing Countries (CTDC-VII) in Sun City, South Africa, sponsored by IUTOX, with the Web URL of http://www.wltox.org. A session at this Congress was devoted to the WLT, and included talks outlining the roles of its partner organizations, plus a panel consisting of several Country Correspondents and a Continent Coordinator (Mohammad Abdollahi (Iran), Sanmi Areola (Africa continent), Ravi Gooneratne (New Zealand), Mary Gulumian (South Africa), Levi Oresh (Nigeria), Salah Soliman (Egypt), Aristidis Tsatskakis (Greece))

Country –Specific and Multi-Lateral Information: Structure, Content, and Navigation

Most of the WLT's home page is occupied by a world map (see Figure 1). One can click on any continent or region, and be led to the page for that geographic area, which presents links to information general to that area as well as to participating countries via their respective flags.

Figure 1. WLT Home page

There are currently over 50 countries represented, with several more under development. Country pages typically contain the following categories of information (see Figures 2 and 3 for sections of the Italy and Iran pages):

- Government Agencies {National and, in some cases, regional authorities.}
- Non-Government Organizations
- Universities
- Professional Societies
- Poison Information/Control Centers
- Miscellaneous Resources
- Key Publications – Books, journals.
- Databases
- Legal Links {Legislation and regulations.}
- About (Country) {News, demography, general country information.}

Figure 2. Italy Page (partial)

- Multilateral Organization Contacts
- Literature References from TOXLINE {Citations to the journals literature, either related to the country or by authors from the country, from the National Library of Medicine.}
- Country correspondents may include other categories as they see fit, and with consultation of WLT staff.

Figure 3. Iran Page (partial)

Language

From the outset, it was understood that language could pose an obstacle to understanding, so a decision was made to make the WLT a multi-lingual resource. Thus, every entry appears first in its native language utilizing the appropriate character sets (e.g. Roman, Cyrillic, Mandarin, etc.).

This is usually necessary and preferred for native speakers within and outside their countries. However, English, which has lately been considered the global lingua franca, certainly of science, is also supplied. Thus, clicking on a non-English language entry will go to the URL for that site. If there is an equivalent English language entry, it will be listed, and hot-linked as well. However, if there is none, at least an English translation of the entry will be listed. While Web sites predominate as the preferred listings, organizational entries not represented by a Web site are included as well. Thus, if no Web site is available, information such as e-mail address, FAX and/or phone number, and mailing address, could be included.

Building Database Content: Country Correspondents

Although a global portal such as the WLT could technically be built from a centralized source, it stands to gain significantly, instead, by inviting contributions from participants representing their respective countries, who would be in the best position to provide complete and accurate information. Therefore, a network of Country Correspondents (CCs) was established. CCs are typically, though not exclusively, scientists engaged in toxicology research or application at governments or universities, who are well acquainted with the toxicological infrastructure in their countries. CCs have been identified via personal contacts and referrals, and are not officially designated representatives of their country governments. In its developmental phase at NLM, the information provided by the CCs were, essentially, funneled through the WLT Project Officer, who reviewed the material and, usually, after several revisions had the IT staff post the country pages. Because information is not static, it became clear that significant resources would be required to update and maintain the portal. An automated link checker, for example, was used to identify broken links, which CCs in collaboration with NLM staff, would repair. There may be any of a number of reasons why a particular Web URL is inaccessible at any particular moment – the organization may have dissolved, the URL may have changed, there may be server problems, the wait time to connect may have become interminably long with the effect being as if the URL is totally inaccessible, etc. Having the CCs take direct control of troubleshooting and repairing such problems, as well as building the pages, as available in the WLT's current platform on Toxipedia, results in a much more efficient operation.

Although Europe represents the greatest number of countries, a special effort is being made to increase participation from other areas, particularly in the developing world, and to offer information which would be of particular benefit to them. Africa is the first region to have a Continent Coordinator, responsible for identifying and working with CCs in the African continent. Country Correspondents and Continent Coordinators are, in essence, the heart of the WLT, for they are in the best position to be knowledgeable about activities in their own geographic regions, and to supply credible information and insight. The value of having a technological edifice supported by a real human foundation is incalculable.

INND/Toxipedia – Collaborative Technology and Security

With the WLT's migration to INND/Toxipedia, a greater degree of control could be placed within the hands of the CCs, in a distributed environment, thanks to the still evolving technology of wiki's. The wiki technology has an interesting history but was first used on the World Wide Web in 1995. Wiki is Hawaiian for quick and refers to the fact that changes are quickly made available to the public. Wiki's are websites that function and grow by public participation and submissions. Wiki's are increasingly recognized by the scientific community as a valuable tool for sharing information and education.2'3 In the case of the WLT, that participation comes directly from the CCs. Every CC registers in the Toxipedia platform. This provides them with access to create and edit pages in the WLT. Once registered, the WLT web manager restricts these editing abilities to their respective country page. The CC and their selected associates can thus rapidly update the pages or respond to suggestions from users or colleagues. This format allows for heightened security on each country page since the only user capable of editing a country's pages is the CC for that country.

The WLT managing staff receives daily reports of the updates made to the WLT. They have the ability to disallow an update if it is deemed inappropriate or irrelevant to the WLT. These operating and security measures allow the WLT to develop under the control of its contributors, with supervision intact at all times.

The Role of IUTOX

IUTOX, founded in 1980, is the world's largest toxicology professional society, representing over 20,000 toxicologists from industry, academia and government, from all six continents, and from 51 affiliated societies. Although it sponsors international congresses and fellowship programs, it recognizes the complementary advantages of the WLT. Specifically, the WLT provides a means of round the clock dynamic exchange across political and geographic boundaries, which could otherwise inhibit in-person meetings. In addition to being a mechanism for information exchange, the network that the WLT is building will provide a fruitful context for capacity building and educational exchange, two of the main goals of IUTOX. Figure 4 shows a map of the IUTOX associated countries and societies and the relative sizes of these societies across the map. A common goal for both IUTOX and the WLT is for toxicologists to be able to identify and contact each other both between and within countries. Among numerous benefits, such recognition can stimulate development of country and region specific societies of toxicology.

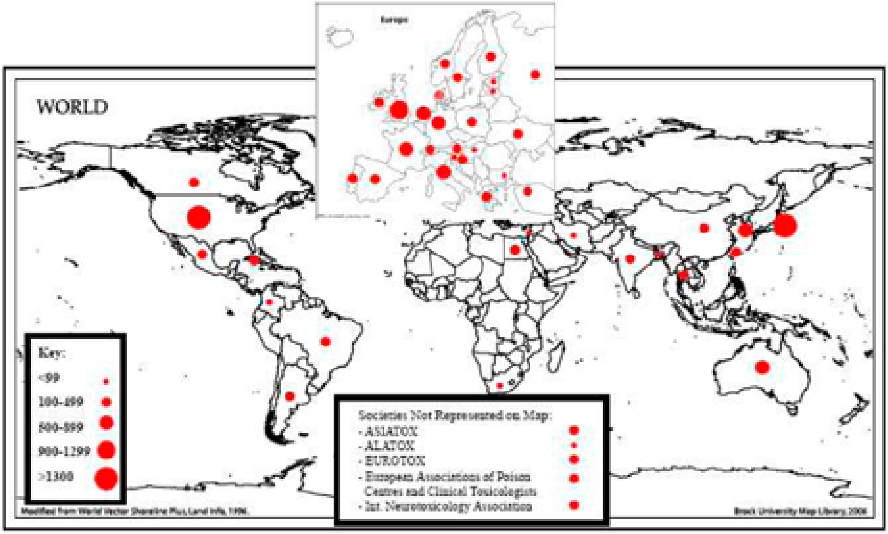

Figure 4. IUTOX Membership

Figure 5. Interactive flag poster

Review – The Advisory Team

Over and above the CCs work, and that of the WLT's partner organizations, another important consideration for the WLT was to assemble an independent review group. Although there had been a nascent steering team at the start of the WLT project, it has become dormant, and the WLT staff is in the process of reconstituting a new advisory group, which will actively review the WLT content and periodically interact largely via conference calls and e-mail.

Tools and Specialized Areas

An important goal is to make global toxicology information more readily accessible to encourage people to explore the global environment and related health issues. To this end, a clickable flag poster with the flags and name of the lead Country Correspondent (see http://toxipedia.org/x/HoBT), was created. The Country flag poster is a pdf file that is easily accessible and will encourage people to explore the countries involved in the WLT (figure 5).

At the request of the Country Correspondents we have begun to create several specialized topic areas and an emerging issues section. The specialized topic areas include teaching resources and ethics sections. As the WLT grows, these sections will become more country specific. The emerging issues section address common priority issues related to the environment and human health. The first two to be identified were e-waste and pesticides.

The Path Ahead

- Expanding the Set of Countries – There are some 200 countries in the world and the WLT was released with an initial set of about 50. This is a respectable start, but much work remains. It is true that some countries will have virtually no toxicology or environmental health infrastructure and others, such as failed states, may be too unstable to include. Nonetheless, there still remain dozens of countries which could make a welcome contribution to the WLT.
- Expanding Features – The WLT staff has developed an extensive wish list of features to enhance the utility of the portal beyond the addition of new countries. These include more robust mapping capabilities, to offer geographical representations of particular toxicology institutes and activities (See Figure 6 for a vision of what this might look like for South Africa); travel awards and fellowships, geared towards developing countries, to help graduate students and/or young researchers attend international meetings; allowing CCs to create their own Web presence on the WLT to offer a more in-depth look at the activities in their countries; creating a newsletter to keep users apprised

Figure 6. Map of Toxicology Resources in South Africa

of developments associated with the WLT and global toxicology in general; creating a kind of chat room/forum or information exchange so that CCs can readily communicate with each other; an educational component will allow syllabi and presentations to become part of the WLT site; incorporate an emerging issues section to highlight toxicological hot topics of concern; continue to explore new and evolving technologies which might improve site navigation and access.

- Funding – An enlarged and stable source of funding is critical for the WLT to be maintained in a timely fashion, updated regularly, and expanded. Needless to say, accomplishing the projects anticipated above will require the WLT to be on a sound financial footing. In that vein, funding sources are being diligently explored. International organizations with like goals are being approached for sponsorship. Another mechanism to be implemented is the creation of two categories of WLT partners – affiliate and supporting. A minimum donation would be required to become a supporting partner.

- Ideas – The WLT welcomes comments and suggestions from the CCs and any other interested parties on how it can be improved. Users and potential users have already been very helpful in guiding the WLTs progress. The e-mail address, Contact@wlt.org, has been set up for this purpose.

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4

STRENGTHENING CAPACITY IN AFRICA

23

Food Security and Social Action for 2050: Building African Capacity

Vivian Lowery Derryck

The world will face a massive food shortage in 2050 if current trends in agricultural production and trade continue. Africa, the continent that will host one fourth of the world's population by 2050, will suffer most acutely. Hampered by climate-related issues such as drought, water shortages and changes in soil nutrients; suffering from massive deficiencies in infrastructure, constrained by inadequate trained personnel and human capacity; and confronting wobbly governance in some nations and fragile peace in many post-conflict countries, Africa has special challenges.

It is in our global national interest to address Africa's challenges, for African agricultural potential, if unlocked, could help alleviate the coming food shortages. According to several recent studies, the world cannot achieve global food security in 2050 without foodstocks from Africa and Ukraine. However, Africa cannot achieve internal food security and contribute to global supplies without fully utilizing the currently undervalued human capacity of its women.

This paper will focus on Africa as a region critical to achieving food security by 2050. In the African context, the paper will discuss food security essentials, identify three major categories of challenges (climate change, infrastructure and human capacity), examine the woeful underutilization of women in agriculture, state the case for a global campaign to achieve global food security and conclude by proposing a constituency-based action plan to help reach global food security by 2050.

The paper advances three related central theses: 1) Africa is central to global food security; 2) sustained food security cannot be solved without a massive global campaign led by civil society that raises awareness of the issue, stokes a sense of urgency and dramatically increases political will among key leaders; and 3) African women are an under-utilized resource whose inputs are critical to solving the global food crisis: If women's efforts are coordinated with the global campaign, the chances for success increase significantly.

Governments, foundations and citizens also realize that food security is the anchor to prosperous lives. Well fed populations amass savings, are healthier, and encourage community stability. Several new initiatives are focused on food security. If these efforts are matched by a robust civil society campaign, we can achieve food security by 2050 or before.

Context

Food security is a focal point of sustainable development in multiple sectors: among them agriculture, environment, economic development, education, health and nutrition. Agriculture undergirds the economies of most countries in the developing world and helps fuel economic growth worldwide. Environmental challenges reduce agricultural yields. Health and food security are linked through nutrition, and educated farmers produce higher yields per hectare.

Food security involves production, access, availability and proper utilization. It also requires an enabling environment of sustained peace and good governance. African is challenged in many of these dimensions. In 2009, Africa saw an overall reduction in per capita food production and insufficient local availability in some countries. African governments spent $40 billion on food imports, an expenditure that is a drain on global food stocks and economically unsustainable in the long-term. In 2010, the enabling environment remains spotty, with active conflicts in a swath of Central Africa and unrest in key states in West Africa as well. Natural and manmade disasters limit food- source sustainability in several countries, while, at the same time, corruption undercuts good governance and undermines effective utilization.

Challenges

African food security faces three sets of challenges. The first is climate change. There is no doubt that Africa is affected more than any other continent. As His_Excellency Professor Bingu Wa Mutharika, President of the Republic of Malawi and Chairperson of the African Union stated at the at the end of the 15th assembly of the African Union in Kampala, Uganda, 'Given that Africa is the most vulnerable region to climate change with the least adaptive capacity, a global partnership to mitigate this is an immediate priority.' He went on to observe, 'The adverse impact of climate change poses serious challenges for African agriculture and food security.' [1]

Climate change challenges included desertification and forest depletion, an array of water-related challenges from drought to water shortages to fisheries depletion to rising ocean temperatures.

Most worrisome is the ongoing nitrogen depletion as $CO2$ leeches nutrients from the soil. The result is less nutritious crops which set off a whole cycle of inadequate nutrition and related illnesses. New programs in orange sweet potatoes and new ways of farming rice are but two promising efforts to combat the soil depletion issue.

The second set of challenges revolves around infrastructure, which can be an inhibitor or facilitator of development. Deficient infrastructure includes outmoded transportation systems, insufficient ports and inefficient or inadequate power utilities, energy sources and ICT. Even with breakthroughs for increased production, marketing and food distribution are hampered by lack of infrastructure. Post-harvest losses due to inadequate infrastructure are a major problem. President Mutharika remarked, 'One of the immediate actions needed is to reduce heavy post-harvest food losses in sub-Saharan Africa estimated at 40 %, compared with less than 1 % in Europe, North America and South East Asia.'[2] In Liberia, forty % of pineapples rotted in the fields in 2009 for lack of transport to processing and distribution centers.

Africa currently spends US$45 billion per annum on infrastructure when it should spend about US$93 billion according to the World Bank.

1. Luncheon Address by His Excellency Professor Bingu Wa Mutharika, President of the Republic of Malawi and Chairperson of the African Union convened at the end of the 15th Assembly of the Heads of State and Government of the African Union, Kampala, Uganda, July 27, 20210.
2. Ibid.

Unfortunately, African infrastructure development costs at least twice the costs in the developing world.[1]

The third set of challenges involves inadequate human capacity development. At the professional level Africa suffers from a dearth of trained agriculturalists and trained researchers. At the farm level, low literacy leads to an inability to participate effectively in agricultural programs. Literacy leads to higher yields per hectare. Human capacity deficits impact infrastructure and climate-change problems, when African infrastructure providers lose $8billion a year to inadequate maintenance, excess staff and under-collected revenues.

In a related human capacity issue, women provide 70 % of the farm labor in Africa, yet in a failure of African governments and donors across the continent, with a few exceptions, women are under-represented in extension services, research, program design, project implementation, training programs, and general decision-making in agricultural and food security initiatives.

According to the World Bank, FAO and IFAD's 2009 *Gender in Agriculture Sourcebook,* gender issues are incorporated into less than 10% of agriculture-related official development assistance (ODA), yet women are key to water management, seed production and distribution, forestry management, value chain management, biotechnology and livestock management to name just a few areas where women could and should have major impact.[2]

Women to the Rescue.

Women are a key to African food security in 2050. Women are the small farmholders producing 70 to 80% of domestic food and women provide 46 to 70% of farm labor, depending on the country. Soil fertility is the largest natural resource in Africa, but soil depletion for the past two decades has resulted in decreased per capita food production. Women are critical to reversing soil depletion, but their roles are not widely acknowledged. Women researchers comprise another potential ally to increase food security. In a landmark program supported by the Rockefeller Foundation,

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1. Vivien Foster and Cecilia Briceño-Garmendia, Agence Française, eds, **Africa's Infrastructure: A Time for Transformation** (N.p.: World Bank, 2009*)* ©2010 The International Bank for Reconstruction and Development.

2. **Gender in Agriculture Sourcebook (**Washington, DC: World Bank, 2009).

Rockefeller found 'that its female grantees produce a disproportionately high number of scientific advances that support positive change in the lives of African farmers.' [1]

There are other impediments to women assuming more effective roles. Land tenure rights and asymmetrical ownership is a major issue in much of the developing world. In Ghana in 2006, women held ten % of land rights, while men held 16 to 23%.[2] In Kenya, woman own five % of titled land, although land tenure rights will change with the newly passed constitution.

In addition to the huge challenge of land tenure, women have lower levels of access to productive inputs (e.g. seeds, fertilize, pesticides, labor); less access to credit to purchase yield-increasing inputs; and limited access to initiatives and special programs. Often the women simply lack necessary background knowledge to be effective participants, perhaps because of their lower levels of literacy. And then there are the hard to quantify cultural factors.

Consider the case of Hawa, a Tanzanian farmer.[3] Hawa and her husband have a small rain-fed farm. Hawa learned of a USAID tree fallow program and wanted to participate. This was not a simple decision. Because of land tenure rights, her access to resources had to be negotiated with her husband. As a result, Hawa's plot was significantly smaller than those planted by men in the program. Not surprisingly, Hawa's plot was less productive. In the end, Hawa dropped out of the program, noting that her husband had planned to take any profit that she would earn.[4]

A campaign for global food security

We need Hawa for 2050, but she is only one piece of the giant mosaic that must be established for food security in 2050. The following is an eight-step plan.

First, we must identify the leadership, men and women who have a vision that they can share. Leaders must also have expertise and integrity. Integrity

1. Rockefeller Foundation Proposal Approval Notification, 2004.
2. **Gender in Agriculture Sourcebook**: 15.
3. A composite based on P. Z. Matata1*, O. C. Ajay2, P. A. Oduol3 and Aggrey Agumya4, "Socio-economic Factors Influencing Adoption of Improved Fallow Practices Among Smallholder Farmers in Western Tanzania", **African Journal of Agricultural Research** 5, no.8 18 (April, 2010): 818-823.
4. **Gender in Agriculture Sourcebook**: 15.

is particularly important in agriculture because of the widespread graft and corruption that often accompanies commodity purchases and distributions. Such a leader is Malawian president Professor Mutharika. He has assumed leadership and spoke forcefully about food security at the 2010 African Union Summit in Kampala, Uganda. He said, 'Excellencies, the high levels of food and nutrition insecurity in Africa are unacceptable. However, this is Africa's opportunity to take out insurance to secure Africa's future. The time for rhetoric has gone. It is time for action to eliminate hunger and malnutrition. It is time for action to increase access to complementary meals.'[1]

Second, leaders must build a constituency. A leader must be able to demonstrate to others the latter's self interest in the outcome the leader is seeking. The President of Malawi spoke of the need for food security by 2015 and described the economic benefits that would come to Africa as a net exporter. Other heads of state could visualize the benefits that would accrue to their populations and the foreign exchange such sales could bring into government coffers.

Third, leaders and constituency must develop a sense of urgency. Food security is a basic human need, so leaders can fashion a universal appeal, describing concrete actions that citizens can take to increase food security. Again, Malawian President Mutharika is exercising leadership as he outlines specific actions that those committed to food security could take. 'Excellencies, it is time for action furthermore to halve the numbers of people living with vitamin and mineral deficiencies. The voices resonating from Africa are clear; they are voices calling for action to position food and nutrition security at the centre stage of development.'[2]

Fourth, leaders must identify the stakeholders who will implement the plan. Stakeholders include farmers' forums, the private sector, ministries of agriculture and ministries of gender and women's affairs, bilateral partners from the donor community such as USAID and DFID, and NGOs from multiple groups including the environment, conservation, health/nutrition and women's empowerment activists. These various constituencies may have histories of working in professional silos rather than reaching out to each other. A successful leader will encourage cooperation by pointing

1. Mutharika, **African Union Summit Address**, July 22, 2010.

2. Ibid.

out intersectoral linkages. He or she might use water as an example, pointing out that water crosses many sectors: an irrigation scheme that is poorly constructed might divert water and set up a breeding ground for mosquitoes. Children playing nearby get malaria. At the same time, some crops are over watered and others, lacking water, shrivel. The commercial value of all crops are compromised and the nutritional benefits of the crop are diminished as well. Water engineers, health care workers, nutritionists and farmers all have a stake in working together.

The fifth step is to identify programs multilateral and country programs currently working on agriculture and food security. FAO, IFPRI, IFAD, CGIAR are four international organizations actively involved in agriculture and food security, while the World Bank and other Bretton Woods Institutions as well as foundations such as Rockefeller and the Bill and Melina Gates Foundation support promising initiatives. Campaign leaders should know intimately programs such as the G8 $20 billion multinational food security initiative pledged at the G8 Summit in L'Aquila, Italy, in July 2009, by the heads of 40 states and international organizations to 'act with the scale and urgency needed to achieve sustainable global food security' and committed more than $20 billion to do so. This should be coupled with the $22 billion requested U.S. Global Hunger and Food Security Initiative. A civil society coalition should take a page from the African Progress Report, a monitoring mechanism set up after the G8 meeting at Gleneagles to track donor fulfillment of pledges made. The coalition should publish annually donor efforts to meet the goals of each initiative.

Africans committed to food security can begin their work with the New Partnership for African Development (NEPAD), the African Union-sanctioned organization charged with the coordination and implementation of continent-wide initiatives to achieve the continent's sustainable development and MDG goals.

NEPAD has three programs that are directly related to food security. For example, the Comprehensive African Agricultural Development Program (CAADP) has focal points in land and water management, market access, food supply and hunger, and agricultural research. A Women's Initiative and Infrastructure Initiative offer two additional major NEPAD efforts where food security could be stressed. African governments pledged to spend ten % of their budgets on agriculture. The majority of countries have not fulfilled that pledge. Civil society can hold leaders accountable through gentle reminders and by publicizing the benefits of investments in agriculture experienced by those countries which have fulfilled the ten % pledge.

Sixth, food security proponents must work with governments. The U.S. has a food security initiative that would benefit from partnering with other efforts. The leadership campaign could explore relations with the U.S. National Aeronautics and Space Agency which excels in environmental mapping.

Following these six steps, leaders will communicate among the groups and document progress. Visible results directly related to investments in agriculture will expand the civil society network. Success breeds success.

Women Lead the Way

But this campaign has to reach African women, the Hawas who form the backbone of African agriculture. A successful action campaign would place women at the center, publicize programs available to women, document the economic benefits of gender partnerships, encourage men to work with their daughters as well as their sons, provide incentives for boys to work on food crops and celebrate productivity gains.

Ultimately, women, through relentless efforts, will lead the way. As a leading African woman agricultural researcher mused, 'When you look at hunger and poverty, it overwhelms and overshadows you. But how do you eat an elephant? A bite at a time. I believe in having an impact. I see hunger and poverty and I'm aware that I cannot solve the problem alone, but I can contribute to solving the problem.'[1]

Conclusion

Food security looms as a key challenge of the next decade. Major initiatives must include Africa as a potential breadbasket and as a continent of acute needs. Africa can overcome challenges of infrastructure and human capacity through investments within the continent. Climate-change related efforts require global inputs. The challenges will not be met and food security will

1. Jeneipher Bisikwa, Lecturer, Department of Crop Science, Makerere University, Kampala, Uganda. An awardee of the Gender and Development Rockfeller Fellowships, 2005-2007.

not be realized without a motivated citizenry across the continent that is mobilized to achieve the goal. Building a constituency requires identifying stakeholders, understanding the dire consequences of inaction, learning the details of various programs of donors, securing a commitment of key stakeholders and harnessing the power of women as pivotal change agents.

Two concrete steps for mobilizing a constituency for African food security are essential: 1) working with NEPAD; and 2) deeply integrating women into research, policy formulation, program design and implementation in food security and agriculture-related initiatives.

Although the picture is sometimes bleak, food security is possible. Notwithstanding, natural disasters such as wild fires in Russia and floods in Pakistan, the global agricultural economy can be harnessed to meet the needs of growing world population. African leaders, the private sector and donors—stakeholders all—are realizing the global stakes and making unprecedented efforts to deepen investments and coordinate initiatives. There is new acknowledgement by Africans and donors of the centrality of food security to long term development and a willingness to examine the relationship of food security to climate change, energy, agriculture and social development (especially health and education). The next step is harnessing the political will and linking it to acknowledgement of the problem, commitment of expertise and resources. Civil society is the vehicle to make the connections, to close the circle, through a grand campaign in which leadership and stakeholders are united by a common vision of food security and concrete steps to achieve it.

Food security by 2050 can happen. President Mutharika of Malawi envisions Africa as a net food exporter by 2015. Urging a continental commitment to food security, he said, 'Excellencies, our people expect us to resolve issues of hunger and poverty once and for all within our lifetime. Posterity will judge us harshly if we do not take action now. If not us, then who? If not now, when?'[1]

1. H. E. Mutharika, **African Union Summit Address**, July 22, 2010.

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Health Biotechnology Innovation in sub-Saharan Africa Through Collaboration with China and India

Andrew Kapoor nad Halla Thorsteinsdóttir

Summary

South-South collaboration has grown significantly over the past decade and can be an important tool to boost development and scientific capacity in Southern countries. With the advancement of the emerging economies China, India, and Brazil we are seeing growing political influence, economic cooperation, and financial ties between these nations and sub-Saharan Africa (SSA). China and India have also been signing high level agreements with SSA nations that emphasize scientific and technological collaboration and have established funds to support the collaborations. While Western media have been sceptical about the interest China and India are showing in SSA little is known about what is driving this collaboration and what opportunities SSA researchers see for these partnerships. Our research investigates the driving forces behind SSA's South-South collaboration with China and India from the perspectives of researchers in SSA and examines specifically research partnerships in one science intensive field, health biotechnology. We identified: the need to test samples and gain access to testing technologies, access to training and capacity-building opportunities, and the wish to advance traditional herbal medicine as key drivers of the

research collaboration. Researchers see mutual interest in collaboration between China, India, and SSA in areas such as traditional medicine, HIV, tuberculosis and malaria. Our study highlights that South-South collaboration in these areas may be a potential mechanism to promote southern led health innovation aimed at developing low cost healthcare products.

Introduction

Biotechnology and genomics research has been customarily pursued by developed nations and it has been the common perception that these types of technologies were better suited to address the health needs of developed countries. However, governments of developing countries are beginning to realize that advancements in health biotechnology can lead to economic, social and health benefits. Several developing countries have undergone rapid economic growth over the past decade including nations such as Brazil, China, India, and South Africa. This economic growth has brought increased trade, technological capacity, and is providing developing countries increasing opportunities to collaborate. Between 1990 and 2000, South-South trade grew at an annual average of 10% in comparison to the world trade average of 6%. A noticeable reorientation of Africa's trade towards emerging markets such as China and India has also taken shape and major African economies such as Kenya, Nigeria and South Africa now list both China and India among their top five trade partners.

We are thus seeing growing political, economic and financial ties between India and China and sub-Saharan Africa and several recent summits and agreements, such as the China-Africa Forum and the India-Africa summit, have placed science and technology among the top priorities.

There is a growing body of literature addressing China and India's presence and trade influence in Africa. Both China and India's collaborations with Africa have been subject to great discussion and debate, their collaborations with Africa have been widely portrayed as being exploitative, and attention is being drawn to the perceived 'threat' their increasing footprint in Africa may pose. However there is neither literature that addresses collaboration in science intensive fields nor research that focuses on the perspectives of researchers in SSA on their collaboration with China and India. Our research investigates the drivers behind sub-Saharan Africa's collaboration with China and India in one science intensive field, the health biotechnology sector. It addresses an important gap in knowledge on South-South collaboration by conducting case study research on China and India's health biotechnology collaboration with SSA. This case study research is heavily informed by interviews with researchers active in collaboration with counterparts in these two emerging economies.

To understand the drivers of the South-South collaborations we carried out case studies in Kenya, Nigeria, and South Africa. The selection of our focal countries was based on our previous mapping research that identified these countries as having the strongest health biotechnology linkages with China and India. We based the case study data collection on collecting information about existing health biotech collaborations we had identified through our previous research to learn from researchers that have had direct experience with South-South collaboration. These case studies relied on multiple sources of data including interviews with 48 experts in the chosen countries (Table 1). We selected interviewees that could provide varied perspectives on collaborations: experts who have been active in research collaborations in the countries of interest, policy makers, directors of R&D institutes, etc. Additionally we relied on background documents, data on co-publications, and other statistics of relevance to the topic to supplement this data. We will briefly present some of the main findings from this work and highlight the most important driving forces behind collaboration between SSA, China, and India in the health biotechnology field.

Table 1. Number of interviews conducted

Countries	Number of Interviews conducted
Kenya	18
Nigeria	15
South Africa	15
Total	48

Main Drivers of Research Collaboration

The need to test samples and gain access to testing technologies, researchers in SSA emphasized the need to fill gaps in their research created by an absence of specialized knowledge and equipment by sending samples to their collaborators in China and India. These included samples such as plant isolates, synthetic compounds they had developed, or other biological agents that needed further analysis. Several researchers at universities and public institutions in Kenya, Nigeria, and South Africa had established these types of collaborations with scientists at the Council of Scientific and Industrial Research in India, citing them as critical to the advancement of their work. These collaborations are mainly in the area of synthetic chemistry, working to increase the activity of isolates identified from traditional African plant extracts. South African researchers have also begun to collaborate with China, sending compounds they have developed to be tested specifically in animal models.

The main reason for the need to send samples to China and India was the dearth of high technology scientific equipment in SSA, particularly in Kenya and Nigeria. Many expressed a need to gain access to equipment such as nuclear magnetic resonance (NMR) and high performance liquid chromatography (HPLC) machines which are critical in the identification of basic compounds, synthetic chemistry, and drug development. One Nigerian researcher emphasized this motivation for sending samples abroad and said 'my samples are being tested in an Indian lab for diabetes, it's much cheaper than conducting the same experiment here… there are so many more institutions (in India) that do animal work it's much easier (there) because here we have to write many applications and it's very expensive'. Although the nature of the technology varied by country in SSA; researchers viewed both China and India as equally suitable collaborators in analysing samples.

Access to training and capacity-building opportunities

Another critical motivator for researchers in SSA to pursue collaboration was the opportunity for research personnel from SSA to visit institutions in China and India for training and capacity-building. Researchers said that the ability to travel to China and India and gain exposure to new information, research strategies, complementary expertise, pool resources and seek scientific advice was necessary to the advancement of their research projects. SSA scientists found counterparts in China and India working on projects more closely aligned with their work in communicable diseases (HIV, TB, Malaria) as well as areas of traditional herbal medicines. Researchers felt these types of expertise were more relevant than the expertise they gained through collaboration with Northern countries: as many of the techniques and strategies had been developed in a resource constrained environment, rather then adapted to a developing context. One researcher commented that

> 'It appears in the western world the focus is different. I would rather, in fact, send a student of mine to India to [a] lab to go and learn some basic things or to evaluate some similar things rather than send student to the US where perhaps we may be rather talking at some very high molecular level, which, I believe, is not the thing that is needed in this environment.'

According to our interviewees, organizations such as the Academy of Sciences for the Developing World (TWAS) have also been key promoters of research exchanges. They have dedicated funds to facilitate both scientific and educational exchanges, which have benefited scientists, particularly in Nigeria and Kenya. These programs have helped scientists across SSA advance their work in Chinese and Indian labs in acquiring new skills and techniques, building capacity, and gaining international experience. The International Center for Genetic Engineering and Biotechnology (ICGEB) has also begun to play a similar role in SSA since setting up a branch in Cape Town to complement its New Delhi, India and Trieste, Italy offices. When comparing China and India, it is apparent that China has been significantly more active than India in providing educational opportunities; whereas India seems to be more focused on providing opportunities for visiting research fellows and professional exchanges.

Advancement and exchange in traditional herbal medicine

Several researchers in SSA expressed a keen interest in developing traditional herbal medicines, and we identified many scientists carrying out collaborative work in this area. Researchers in all three SSA countries cited the economic benefits that could be realized through the licensing and commercialization of compounds screened for drug development in India or China. However, interviewees emphasized that although SSA has a strong culture of traditional medicine; this remains informal and lacks the scientific grounding needed to exploit its potential value. Researchers in SSA identified India particularly as a key partner in helping African scientists build the scientific base for a traditional medicines industry. Scientists underscored that collaboration with Indian scientists and institutions and to a lesser extent the Chinese, has built capacity and advanced African knowledge and expertise in this area.

Our research highlighted specific areas of collaboration in traditional herbal medicine which can be grouped broadly into two areas: isolation and screening of active constituents in plant extracts; and analysis or synthesis of compounds. Interestingly, South African researchers engaged in a different type of collaboration with respect to herbal medicine. They preferred joint work where they could learn from Indian counterparts about regulation, patent protection issues, standardization of traditional medicinal products, management of traditional knowledge databases, distribution of benefits and the prevention of exploitive science. India has made strides in helping South Africa set up an electronic database to manage traditional knowledge comparable to the one set up by the Center for Scientific and Industrial Research in India.

Conclusion

This research has illustrated that there are strong motivational factors behind the pursuit of SSA's collaboration with China and India that are likely to strengthen health biotechnology development in SSA. Our interview data suggests that South-South collaboration may be a potential mechanism to promote southern led health innovation. The fact that China and India have already built up scientific and technological capacity in the health biotechnology field opens up the door for SSA collaboration among these countries. By having both research infrastructure and knowledge in this field, China and India can play an important capacity building role in SSA. It is not only their differences that make China and India valuable for SSA; similarities with regards to shared health problems and the need to develop low cost health solutions, affordable to their populations, also drive their collaborations.

Our research showed further that collaboration in traditional medicine was of great interest to the SSA health biotechnology field. Africa's untapped biodiversity, rich history of traditional medicine, and common ground with China and India in this area may provide fertile grounds for the innovation of new health products. Many researchers in SSA cited this as a primary avenue through which to strengthen collaboration with China and India, especially in the development, advancement, and commercialization of local traditional knowledge. Thus it highlights an important sub-field within health biotechnology where a focus on supporting collaborative initiatives has a relatively high potential to lead to innovative health solutions. Governments and other institutional actors promoting SSA development should pay attention to this opportunity and devise strategies for promoting collaboration based on harnessing traditional medicine. They should also pay a close attention to what can be done to strengthen the potentials of the collaboration to lead to innovation in new health products or services.

Our case study research examining the drivers behind SSA's health biotechnology collaboration with India and China illustrates some of the important factors that shape South-South collaboration in this field. Understanding the drivers behind the collaboration between SSA, China and India is the first step towards understanding what role they can play in strengthening knowledge production and innovation within developing countries. However, further studies need to be undertaken to explore in more detail strategies and policies that can support collaboration among these countries. Leveraging these strategies and policies will be important if South-South collaboration is to deliver on its potential to strengthen health biotechnology development in SSA.

Acknowledgements

The authors thank all the researchers, and other experts that took part in this research and generously shared their knowledge and time.n This project was funded by Genome Canada through the Ontario Genomics Institute and by the International Development Research Centre, and was supported by the McLaughlin-Rotman Centre for Global Health, an academic center at the University Health Network and University of Toronto. H.T. is supported by a New Investigator Award from the Canadian Institutes of Health Research.

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The African Biosafety Network of Expertise (ABNE)

Betty Kiplagat

In a drive to harness Science and Technology for Africa, African leaders have adopted a Science and Technology Consolidated Plan of Action (CPA) as a framework for a science and technology agenda for the continent. The CPA has 13 research and development program areas, namely biodiversity, biotechnology, indigenous knowledge and technology, energy, water, desertification, material sciences, manufacturing, laser technology, post-harvest technologies, information and communication technologies, space science and technologies and mathematical sciences. The African Biosciences Initiative (ABI) is the first cluster of these flagship programs, and comprises biotechnology, biodiversity, indigenous knowledge systems and technology.

Under the NEPAD African Bioscience Initiative, four biosciences networks have so far been established on the basis of geographical delineations as follows: the Southern Africa Network for Biosciences (SANBio) for Southern African countries; Biosciences Eastern and Central Africa Network (BecANet) for Eastern and Central African countries; West Africa Biosciences Network (WABNet) for West Africa countries, and North Africa Biosciences Network (NABNet) for North African countries. Research and development in Biosciences is carried out at regional levels through the above regional biosciences networks, which comprise institutions and laboratories that have agreed to share their infrastructures and human resources. A regional biosciences network consists of a hub with several nodes distributed throughout a region. The choice of a hub is determined by the availability of an institution (within a specific region) that is actively involved in scientific research in biosciences, while the nodes are other institutions in the regions that are also involved in biosciences research in specific areas where they have comparative advantage.

In the flagship program of biotechnology, the four ABI networks mentioned above carry out several research programs depending on priorities identified by the regions. This arrangement is in line with the consultations that were carried out by the NEPAD Office of Science and Technology (NEPAD OST) in 2004 and 2005. The approach is such that each region has a core mission to fulfill based on the existing strengths, expertise and experience it already possesses in biotechnology research and development. The core missions identified for these regions are as follows:

- Southern Africa: Health Biotechnology
- Central Africa: Forest Biotechnology
- Eastern Africa: Animal Biotechnology
- Western Africa: Crop Biotechnology
- Northern Africa: Pharmaceutical Biotechnology

Safe Use of Biotechnology in Africa

In order to effectively advance the science of biotechnology on the continent, Africa needs to adopt a co-evolutionary approach in which the function of regulation is to promote innovation, while at the same time safeguarding human health and the environment. In the light of such a safety-conscious approach, the African Ministerial Council on Science and Technology (AMCOST) has resolved to develop a 20 year biotechnology strategy whose specific regional technology goals will be implemented through Regional Economic Communities (RECs). All this would ensure the promotion and application of regional regulations which would, in turn, guarantee a safe use of modern biotechnology. A key element in the resolution is a need to develop regulatory systems in which there is a balance between promoting learning and creativity and protecting public interests.

The lag in development of a governance capacity for biotechnology is apparent in the current status in the development of National Biosafety Frameworks (NBFs). Eighty nine percent of African countries that are signatories to the Cartegena Biosafety Protocol have been making slow progress towards developing the key Components of the NBF which comprise of:

- A policy on biotechnology
- Laws and regulations on biosafety constituting a regulatory regime for biotechnology
- An administrative system for handling applications and issuance of permits
- A mechanism for public participation in biosafety decision-making

The constraints of inadequate policies and legal frameworks noted above are a concern and therefore need urgent attention. To that end, it is none other than Africans who should address such concerns in order to achieve credibility in the eyes of African governments, the African civil society, and the African peoples.

While science is moving forward, the inability to evaluate the potential environmental and food safety risks (that might be posed by biotechnology-derived products is delaying decisions about whether or not to utilize these products) in Africa. There is no credible resource base currently available to decision makers that would provide science-based regulatory data and information with a focus on biotechnology products for Africa. There are many projects and programs focusing on building biosafety capacity in various countries on the African continent. However, most of these projects and efforts are time-bound, country-focused and targeted to specific crops and technologies.

The Need for Biosafety Regulatory Capacity in Africa

One of the main weaknesses in implementing these programs has been inadequate capacity building and the transfer of knowledge and information from project proponents to the implementing agencies and the beneficiaries. As a result, many of these projects collapse at the end of the project cycle, leaving a gap in terms of skills transfer. In addition, the exit and succession plan is either not clearly articulated or not included in the project design. In a nutshell, there is no network of expertise that is Africa-based and Africa-driven to support the development of regulatory processes and their implementation in individual countries.

In many African countries, the low level of human resource capacity means that a focus on skills development and capacity building should be given priority. Such a capacity building program would build the confidence of the participants in order to empower them to eventually manage future projects on their own in their countries. This state of affairs would allow for a "buy in" from all stakeholders.

Why ABNE?

To address the problem of a lack of expertise and experience, as well as limited networking among the available expertise and institutions on the continent on biosafety, NEPAD Office of Science and Technology has established an African Biosafety Network of Expertise under ABI. The network shall be tailored to national and regional needs in order to optimize the use of available expertise, resources and infrastructure at national, regional and continental levels and, where need develop additional capacity and linkages.

What will ABNE do?

Given that there are several initiatives that are currently involved in capacity building in biosafety on the continent, ABNE will consolidate the work of these initiatives so that progress is monitored and the developed capacity is effectively and adequately utilized. A unique feature of ABNE will be to provide technical assistance, biosafety related tools and resources to members of the National Biosafety Committees (NBC), the Institutional Biosafety Committees (IBC) and staff of the plant quarantine agencies (PQs) so that the members are better able to make their own science-based regulatory decisions towards implementing national biosafety regulatory frameworks. These regulatory support services will be provided through designated regional and continent-wide nodes.

In addition, an added value of the ABNE is that, through the AU/NEPAD agenda, the Network will support the national regulatory frameworks to become functional by providing back-stopping services on a need basis. The ABNE, being an African-based network, will build the capacity of national, regional and continental regulatory institutions through the RECs in a sustainable manner rather than on an ad hoc basis, as is currently the case. This will be done through designated regional nodes which will provide such services. The ABNE, through the African Union Commission, will also provide evidence-based information to countries, RECs and African Union Summit. This information will inform policy on harnessing biotechnology for Africa's development.

Participation in ABNE

Participation in the ABNE activities is open to national, regional and continental institutions, public and private organizations that are willing to share their expertise, facilities and other resources with the Network. Participation in the ABNE will be through the activities and services conducted at sub-regional nodes and/or through other programs and organizations participating in the Network.

Public and Private Partnerships

Limited involvement of public and private institutions in biosciences R&D has been identified as one of the key factors that have contributed to Africa's falling behind in biosciences. The private sector can now be engaged through the existing NEPAD Business groups. In addition, the ABNE will directly engage the same sector in its R&D programs by building internal collaboration and linkages on the continent.

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Barriers to Health Technology Development and Commercialization in Sub-Saharan Africa

Kenneth Simiyu

Despite global progress made in improving the health of people and increasing life expectancy, Sub-Saharan Africa (SSA) continues to be plagued by many health problems. Commercialization of health products from Sub-Saharan Africa presents opportunities to solve some of these health problems but it faces enormous challenges. Health product commercialization is poorly understood in the African context. In this paper, barriers to health product commercialization in sub-Saharan Africa are investigated. The framework of analysis is innovation systems, which is central to health product commercialization. Case study methodology is used, aimed at providing a rich picture of what is happening in sub-Saharan Africa with respect to health product commercialization. The results indicate that many barriers identified are the same that exist in other parts of the world but they are amplified in Africa because of weaknesses in the overall national innovation systems. These weaknesses include infrastructural weaknesses such as limited internet connectivity due to low bandwidth and high costs, constant interruption of power supply, poor telephone communications and the absence of technical support from skilled technicians.

Introduction

Innovation and deployment of locally developed health technologies in Africa has become a major subject of discussion as one of the ways that can lead to improved health indicators. Momentum has been building steadily, predominantly through production of policy and technical documents (Chataway et al., 2009). This momentum has also been the focus of discussion at nearly all major international events discussing global health e.g. the global ministerial conference on research for health ministers, as well as reaching the highest political levels including the African Union heads of government meetings as well as the annual G8 meetings.

New health technologies vary from new drug molecules of traditional plant remedies, vaccines, medical devices, and diagnostics, as well as new techniques in process engineering and manufacturing, management approaches, software, and policies in health systems. However, in the context of developing countries, new technologies need not necessarily be novel to the world but novel to that particular setting. This may include standardization and providing the scientific basis of traditional plant remedies or adoption of technologies developed elsewhere to local settings.

Some promising technologies with origins within Africa's research institutions are already having an impact. An example is the Hepcell Kit developed at the Kenya Medical Research Institute (KEMRI) for point of care diagnosis of hepatitis in low resource settings. This kit is inexpensive but effective and the advantages over other testing kits include the fact that its reagents are produced domestically; it does not require electric power hence can be used in rural settings and the results can be viewed without the aid of a microscope (Juma & Serageldin, 2007). Other examples include phyto-medicine products like Niprisan®, used to treat sickle cell anemia, from Nigeria's National Institute for Pharmaceutical Research and Development in Abuja and the commercialization of products from the Neem tree by scientists at the Kenyan-based International Center for Insect Phyisology and Ecology (ICIPE). There may be many more examples that exist, but barriers may be preventing there commercialization.

Globally, many technologies have failed to reach the market for lack of exposure, or for financial and strategic reasons and hence this is not unique to Africa. While these technologies are potentially valuable assets, they have 'stagnated' within the organization which developed them and are not being effectively exploited (Ehretsmann, Hinkly, Minty, & Pearson, 1989). Ehretsmann, et al (1989) state that in the UK, this situation is typified by organizations whose *raison d'etre* is not to produce commercial products i.e. higher education establishments or publicly funded research establishments such as the Ministry of Defence. Because commercial products are not the organizations' goal there is little incentive or drive to develop them. This situation has been recognized for some time and organizations such as the BTG (British Technology Group) and the DTE (Defence Technology Enterprise) have been established to aid the commercialization of research carried out in universities and in MoD research laboratories.

Suffice to say, a lot of scientific research is being carried out in Africa's academic and health research institutions and the principle constraint to greater impact is not so much a lack of scientific excellence or expertise, but rather the failure to harness research findings and bring them to the market (Forum for Agricultural Research in Africa (FARA), June 2004). The discourse on domestic innovation being crucial to improving health indicators in sub-Saharan Africa has however not been backed by evidence of potential technologies that may be commercialized. In Sub-Saharan Africa, systematic studies to identify technologies that can be commercialized have not been done thus it is difficult to quantify and analyze the potential impact of Africa's domestic health innovation.

This paper uses data obtained from scientists working in laboratories in Ghana, Kenya, Nigeria, Rwanda, Tanzania and Uganda to highlight the challenges that scientists face in their attempts to commercialize technologies. The study arose as a result of preliminary studies on health innovation systems in these countries by the McLaughlin-Rotman Centre for Global Health, Canada. During these studies on health innovation systems, researchers from the MRC came across promising locally developed technologies that, if replicable, would provide solutions to some of Africa's health problems while at the same time generate profits for African scientists. Examples include a locally developed Malaria diagnosis kit in Tanzania. However, these technologies were not being commercially exploited. Because of this, it was thought that there could be other technologies out there in Africa's research institutions which are not in the public domain, and whose inventors have no idea what to do next, yet have very great potential for social impact and economic value. This gave rise to the need for a systematic evaluation of what may exist in these institutions.

The study focused on technologies in African research Institutions which have failed to reach the marketplace, for reasons which are connected more with the environment in which they were developed or external factors (like policy, finance etc), than with the technology itself. They are referred to as stagnant technologies.

Research Methods

In this study, the design and analysis was qualitative (Denzin & Lincoln). Case study research methodology (Yin, 2008) was used. The philosophy behind the case study is that sometimes just by looking carefully at a practical, real-life instance a full picture can be obtained of the actual interaction of variables or events (Kõomägi & Sander, 2006). The case study allows the investigator to concentrate on specific instances in an attempt to identify interactive processes that may be crucial but that are transparent to the large scale survey. It is then possible to illustrate the links between various variables and provide a three-dimensional picture of the situation.

Data was collected through reviews of academic literature and policy documents and through open-ended, face-to-face interviews in the respective countries. An initial pool of participants was selected through literature search and review of online documents and this was based on their research activities. They were then contacted via email. Although bibliometric indicators show that publications from the continent were less than 1 % of the world's total (UNESCO. Institute for Statistics (UIS), 2009), this alone cannot be used as a good indicator of available scientific capacity nor of the innovative capabilities of institutions. Not all scientists in Africa publish and even when they do, most do so in little known regional journals thus there work may escape the radar if other techniques, e.g. an internet search or surveys, were used. This necessitated visits to institutions and face to face interviews with the scientists. Using semi-structured interviews, participants were invited to discuss their research activity with the focus on products that they may be developing. There was no pre-determined time limit or limit to the number of products that the interviewee wanted to discuss. Snowballing was then carried out whereby the original participants referred us to other scientists whom they considered should be approached based primarily on their research activities. Interviews were digitally recorded and subsequently transcribed. Coding and thematic analysis (Corbin & Strauss, 2008) was then carried out by the lead author.

An ideal product development pathway encompasses a drug, biological product, or medical device moving from basic science, through an evaluation process (prototype design or discovery) to clinical trials and full scale development of the product and acceptance by users. Thus the interview questions revolved around identifying the technology, the application, and evaluation of their clinical benefit, safety, and cost-effectiveness relative to existing alternatives and the barriers to their commercialization.

Discussion

There are a wide range of health products being developed in African countries. The most advanced health products being developed are drugs from traditional plant medicines. But in addition to this, medical devices, vaccines and diagnostics are also being developed.

The World Health Organization (WHO) estimates that up to 80% of Africans rely on traditional plant medicine as their primary source of medication (WHO, 2002). Some African phytomedicines, like Hoodia from South Africa, are well known in the international market and so supply economic benefit for the producing countries. Many authors have documented traditional plants of medicinal value in Africa and include Okigbo (2006) who in a study found that the main illnesses targeted by African herbal medicine are identified as: Malaria, infectious gastroenteritis, diarrhea, dysentery, diabetes, measles, meningitis, tuberculosis, HIV, pneumonia, smallpox, gonorrhea, tropical ulcers, schistosomiasis, filariasis, onchocerciasis, trypanosomiasis, worms (especially Guinea worm), tachycardia, fibroids, palpitation, back pain, and snake-bites (Okigbo & Mmeka, 2006).

There are few medical devices being developed and commercialized locally. They usually represent products of low manufacturing complexity using locally available raw materials like cotton and plastic material (IFC, 2007). The International Finance Corporation (IFC) published a report in 2007 which showed that medical devices that are currently produced in SSA include disposable syringes, surgical gauzes and padding material. Other devices include mosquito nets-especially the long-lasting insecticide treated mosquito nets (LLINs)—with the most notable manufacturer being A-Z textile manufacturer in Arusha, Tanzania.

Barriers to Technology Commercialization

Discussions with scientists in Africa reveal that there are very many barriers to commercialization of their ideas. Some of these barriers occur at the laboratory stage i.e. insufficiently developed technologies. Many barriers identified, however, are as a result of the institutional setup in which these technologies are being developed. Many of the issues identified in this study are cross cutting among scientists in academic institutions, research institutions and private companies undertaking R&D.

While these same barriers exist in other parts of the world, they are amplified in Africa because of weaknesses in overall national innovation systems. These weaknesses include infrastructural weaknesses like limited internet connectivity due to low bandwidth and high costs, constant interruption of power supply, poor telephone communication and the absence of technical support from skilled technicians to support the scientists.

Some of the barriers identified in this study include:

Lack of proof of concept funds

Many scientists cited the absence of funds to support research beyond basic research. In sub-Saharan Africa, there are no venture capital firms investing in health. Thus there are no funds to support proof of concept and scientists are often forced to use their own money if they want to develop a product. And traditional bilateral donors are reluctant to support research beyond basic research. And even when there are globally available funds, e.g. from philanthropic foundations, most funding has ends up benefiting scientists in the developed world. Funding health innovation in Africa has largely been left to African governments themselves, supported by donors, but this has been indirectly through various innovation funds that exist such as the Millennium Development Fund in Uganda and the Innovation Fund in Kenya and Ghana but since these are not specific to health, most of these have ended up going to projects in fields such as engineering.

Intellectual property

Intellectual property management is another area that hinders the further development of technologies. Many scientists do not patent their work because they are not skilled enough to identify technologies that they can patent. At the same time, the costs of patenting are beyond the reach of many scientists. Besides, institutions do not have the necessary structures to support patenting of intellectual property. These structures include the absence of technology transfer offices and intellectual property (IP) policies. Lack of IP policies discourages scientists from innovation because the shared benefits are not clearly spelt out.

Focus on publications not products

Traditionally, most universities and research institutions have emphasized publications as the best indicator for performance. Most of these institutions have not prioritized commercialization of their research. As a result, scientists have concentrated on publications, regardless of the impact of their research on people. Many scientists interviewed cited this as a major hindrance in product development. However, a few institutions have now introduced new benchmarks to evaluate performance, including innovation.

Poor marketing ability

Most of the scientists interviewed have no training in business. Hence most have no idea how to identify the potential market of their technology nor did they know how to seek venture capitalists or private sector investors. Thus their technologies have stagnated in the laboratory.

Lack of equipment

Most institutions in Sub-Saharan Africa lack the necessary equipment required for drug analysis. During the study, we identified only three institutions, two in Kenya and one in Ghana, in the whole of sub-saharan Africa with nuclear magnetic resonance spectroscopy (NMR) machines that are necessary for understanding protein and nucleic acid structure and function and hence identify molecules. The maintenance cost of these NMR machines was also beyond the reach of many of the institutions. Similarly, very few institutions posses HPLC equipments, which are necessary for characterizing drug molecules.

User acceptability

User acceptability of locally developed technologies still remains a challenge. Part of this is due to aesthetic reasons while in some other cases it is due to perception. Packaging of products, especially of traditional plant products remains challenging. Bottles, for example in Uganda, have to be imported and local substitutes are not appealing to the eye. Very little attempts have been made to educate the public on the advantages of locally developed technologies.

Conclusion

There is great potential in the development of local health products in Africa if proper investments would be carried out to overcome barriers. As this study has shown, there are many barriers to commercialization of technologies lying in laboratories in Africa.

The increased discourse of domestic health innovation as being the panacea to sub-Saharan Africa's declining health indicators and one of the most important 'input' of any health system has often been in sharp contrast with the volume of resources that would be required to develop these technologies.

The significance of this study is that it provides the evidence needed to support the on going discourse of domestic health innovation. Much more research work needs to be done to identify more technologies and developing models that can be used that minimize some of the barriers identified. Picking potential winners from a vast range of opportunities is a tricky and risky business and there is need for potential investors to discuss further with concerned scientists. At the same time there is need to develop a framework that could help in the assessment, prediction, and identification of those technologies with above average potential for commercial application. Development and enforcement of non-disclosure agreements would motivate scientists to disclose more of their technologies, thus enable investors make informed choices. These then can receive targeted funding.

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Building Natural Products Expertise in Southern Africa

E Jane Morris and John D K Saka

This paper describes the successful establishment of a regional network involving four countries in Southern Africa to train post-graduate students in natural products research, in order to strengthen the universities in the region. In addition, a number of policy and support interventions are being put in place to ensure that the research generates meaningful outputs that can contribute to improving health, nutrition and food security in the region.

Introduction

In 2008 a call for proposals was launched by the Science Initiative Group at the Institute for Advanced Study at Princeton University. With financial support from the Carnegie Corporation, the aim was to create a number of networks to implement a Regional Initiative in Science and Education (RISE) in Africa, to train the next generation of university faculty members at MSc and PhD level, and to enhance the qualifications and support the retention of existing university faculty.

The SABINA network (Southern African Biochemistry and Informatics for Natural Products) was established as one of five RISE networks in response to this call, and was granted financial support towards the end of 2008. It comprises institutions in South Africa (CSIR, University of Pretoria and University of the Witwatersrand), Namibia (University of Namibia), Malawi (University of Malawi and the Tea Research Foundation of Central Africa) and Tanzania (University of Dar es Salaam). The Academic Director of SABINA is Prof JD Saka from the University of Malawi, and the University of Malawi also acts as the coordinating institution. SABINA exists to train both PhD and MSc level scientists through research in the biochemistry and chemistry of natural products, including bioinformatics as an essential tool for data management and structure-function elucidation.

In 2009, additional funding was obtained from the European Union's Africa-Caribbean-Pacific science and technology programme for a number of policy and support actions that would complement the SABINA programme. Further, co-funding was also received from the South African Department of Science and Technology. This new project, known as POL-SABINA, is coordinated by the University of Pretoria in South Africa and led by Prof Jane Morris of the African Centre of Gene Technologies

The Importance of Natural Products

Over a number of years there has been a considerable amount of research into natural products (primarily plants and fungi) that has been undertaken in Southern Africa, particularly on medicinal plants (Light et al, 2005). Emphasis has been placed on the value of indigenous knowledge concerning the region's vast biodiversity. Traditional healers are widely consulted and make extensive use of plant derived medicines. There is also considerable interest in indigenous fruit and vegetables that appear to have health promoting properties (e.g. Jansen van Rensburg et al, 2007; Azam-Ali et al, 2001). Other plants have potential application in agriculture as insecticides etc. Non-indigenous crops, such as tea, that are commercially grown in the Southern African region are also being investigated to enhance their health promoting properties (Sharma et al, 2007).

Natural products are gaining increasing popularity around the world as an alternative to, or as a supplement to, chemically pure pharmaceuticals. In the developing world, plant-based remedies have always been the mainstay of traditional healers. Natural products are these days moving into the formal marketplace (Makunga et al, 2008) but it is essential that their properties should be well characterized and their efficacy and safety should be established and confirmed.

The Need to Develop Expertise in Natural Products Research

Developing countries suffer from interlinked problems of poor health, malnutrition and lack of food security. While it is clear that natural products can play a significant role in alleviating these problems, it is essential that scientists in developing countries must be partners in finding solutions, not just recipients of products developed elsewhere. This can only occur if the universities and their cooperating research institutes in the region are significantly strengthened and well-trained faculty members are retained and supported to develop a meaningful career in research and education.

The SABINA programme is currently training seven PhD students and six MSc students in a variety of areas of chemistry, biochemistry, molecular biology and bioinformatics, all based on various aspects of natural products research. The integration of disciplines and techniques in natural products research is demonstrated in Figure 1.

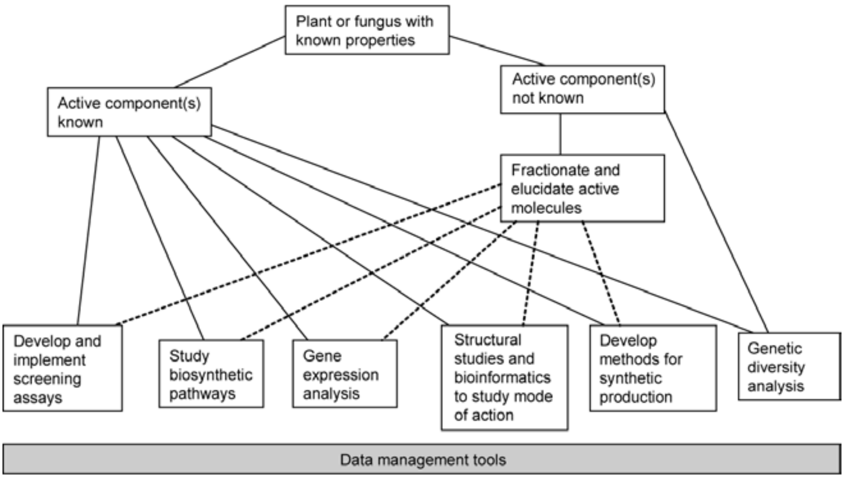

Figure 1. The Integration of Natural Products Research Components

The majority of students in the network already have faculty positions in their home institutions, to which they will return at the end of their studies. Students are encouraged to register for their degrees in a different country within the network, in order to promote interaction and exchange.

Through this networked approach, SABINA is encouraging the sharing of skills between institutions and across disciplines. Students and supervisors are encouraged to spend time in the laboratories of other institutions within the network, particularly in order to gain access to equipment or to learn techniques that may not be available in their home institution.

To support the networked approach, a web-based Virtual Research Environment (VRE) is being developed with POL-SABINA funding. Globally, electronic media are facilitating new ways of collaborative research, of disseminating results as well as the multidisciplinary use and re-use of research outcomes. For a variety of reasons this new paradigm shift has not previously reached Africa in any holistic way, but this situation should now be rectified by means of the current activities. The sharing of knowledge needs to occur in a variety of areas including literature review, funding opportunities, proposal writing, project management, scientific workflow, training and mentoring, report writing etc.

Moving from Research to Implementation: The Challenges

Although the SABINA partnership is proactively training scientists in the development of natural products, the capacity, knowledge management systems, supportive policies and understanding of the requirements of the full value chain are not fully in place (either institutionally, nationally or regionally) to support the desired outputs of excellent science and technology that can be translated into sustainable development and economic growth.

To achieve real outputs, it is necessary to create a critical mass of expertise across the whole innovation chain, from discovery to development and implementation. While scientific expertise needs to be built first in the universities and research institutes in the region, this needs to be linked to knowledge of intellectual property, indigenous knowledge systems, farming systems, entrepreneurship and commercialization. Unless all these components are in place, and supported by appropriate government policies, research will remain an interesting academic exercise but will do little to address real problems.

With support from POL-SABINA, interactive workshops will be organized in each of the network countries, to facilitate the interaction between policy makers, scientists, farmers, traditional healers, holders of indigenous knowledge and entrepreneurs and to discuss the need for appropriate policies and legislation in the area of natural products. At each of the workshops a situational analysis will be undertaken, coupled with a needs analysis, and an action plan will be drawn up to prioritize policies and legislation that are needed in each country.

In order to develop a wider range of expertise and know-how, a number of courses are being organized covering project management, fund management, research methodology, intellectual property management, commercialization and entrepreneurship. Courses on particular techniques or fields of research are being offered for network participants such as chromatography and phylogenetics.

Subsequent to the training in commercialization and entrepreneurship, seed funding will be provided to enable the development of an implementation plan for a promising project to be selected on a competitive basis.

A facility is being created at the Tea Research Foundation in Malawi where it will be possible to grow quantities of test plants under controlled conditions to demonstrate their qualities to farmers and agro-industries. A pilot scale GMP (Good Manufacturing Practice) botanical supplies unit is already in place at the CSIR in South Africa. The potential application of the research can thus be demonstrated to farmers, agroprocessors and entrepreneurs at open days, and all relevant players in the value chain will be engaged in the product development process.

Management of Intellectual Property

Intellectual property (IP) issues around natural products are a cause for concern, considering that many plants with useful properties are found in more than one country in the region, and the traditional knowledge concerning their use may also not be specific to a particular country.

In the context of the SADC region, regional leaders have resolved to take a common approach to address issues pertaining to IP management. Article 2 (m) of the SADC Protocol on Science and Technology has the objective of fostering co-operation and promoting, the development, transfer and mastery of science, technology and innovation in Member States in order to enhance and strengthen the protection of intellectual property rights. Further Article 4 commits member states to cooperate in science, technology and innovation in the area of harmonization of policies and regulatory frameworks including emerging new technologies. In response to the SADC S&T Policy, the NEPAD Secretariat through its regional Network (SANBio) is proposing the establishment of a High Level Panel on IP Management in the region. It will be a body of eminent experts to advise the SADC Secretariat, its Member States and various organs, on current and emerging issues regarding IP and the use of biological resources, particularly as they relate to public sector research, to developing countries, and addressing the urgent health and agricultural needs of the people of the region. A particular area of interest for NEPAD/SANBio is in building the capacity to manage intellectual property and biological resources in the countries of the region.

There have been many workshops and conferences in the region and on the continent on IP issues but to-date no functional policy is in place in any of the countries in the region and there has been no progress towards harmonization.

With funding from POL-SABINA it is planned that the High Level Panel on IP Management will produce a report for adoption by the SADC Ministerial Conference on Science & Technology (SAMCOST) and later by the SADC Heads of State. Once the Heads of State and Government have adopted this policy/protocol, then efforts would be directed at helping countries to domesticate it. The task of the Panel is to engage in a process of connecting with the political leadership which has already shown willingness to address IP issues through the SADC S & T Policy.

Conclusion

Through the SABINA and POL-SABINA programmes, it is envisaged that the participating scientists will have gained increased capacity to undertake meaningful research in a conducive environment; small-scale farmers will be enabled to diversify their crops and gain greater added value; holders of indigenous knowledge will have their knowledge respected and rewarded; local entrepreneurs will be encouraged to start new enterprises based on natural products, and consumers will benefit from products with enhanced nutritional or health promoting properties, or that have specific medical applications.

Acknowledgements

Funding from the Carnegie Corporation of New York to support the SABINA RISE network is gratefully acknowledged. In addition the support provided by the Science Initiative Group at the Institute for Advanced Study has been invaluable.

Funding received from the European Union Africa-Caribbean-Pacific Science and Technology Programme to support the POL-SABINA project is gratefully acknowledged, as well as the co-funding provided by the South African Department of Science and Technology.

The valuable work of the project managers for SABINA (Mr Frank Ngonda) and POL-SABINA (Ms Ella Nyakunu), the support of the host institutions (University of Malawi and University of Pretoria), as well as the active participation by scientists in all the participating institutions have all contributed to the successful building of the network.

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Translational Medicine at South Africa's Medical Research Council

Anthony Bunn, Louis Rossouw and Maritha Kotze

The article describes how the major advances in engineering and biology over the last five decades are now combining to revolutionize the practice of medicine and health care. The authors have devised four general rules that appear to be the major drivers moving health care from the present symptomatic, disease-focused endeavour to so-called digital or P4 medicine. As a result of recent legislation and policy directives in South Africa, the South African Medical Research Council has assumed a positive role in converting translational research into health care practice. This is being achieved, inter alia, through on-going translational research and open innovation in molecular genetics and bio-informatics.

Introduction

Two major revolutions are transforming medicine from a disease driven, treatment-based discipline to one that will rely on both clinical and molecular genetic risk assessments. This will lead to personalised interventions to mitigate risk and promote health and personalised comprehensive care when required. This results from the synergy of recent remarkable advances in engineering and biology and more specifically from the explosion of information and knowledge brought about by information and computer technologies (ICT) and genomics. Over the next few decades we expect to witness this transition from disease focused medicine through translational research and translational medicine to so-called P4 medicine (predictive, preventative, personalised and participatory).

In its simplest form, translational medicine results from the emphasis to integrate medical research outputs from the basic sciences, social sciences and political sciences with clinical investigation to optimise both patient care and preventive measures that will extend beyond the provision of healthcare services and include patient participation in their own health. This paradigm shift in medicine is being driven by the early adopters of the ICT and genomic revolutions and by the ability of people to have rapid and easy access to medical websites and to participate in health related discussion forums using the internet.

Research and Innovation in South Africa

South Africa and Egypt share interesting geographic positions being located at the most southern and the most north-eastern regions of the African continent respectively. Both also share the two highest GDPs in Africa. The Gross Expenditure on Research and Development in South Africa is just less than 1% of GDP which equates to about $2.5 billion. This represents about 0.5% of global research.

In terms of health, SA suffers from a quadruple burden of disease- namely HIV/AIDS (6 million of 48 million population), malaria, TB and the emerging epidemic of non-communicable diseases (stroke, heart disease, diabetes and cancer). The latter is predominantly induced by large-scale urbanisation and the lifestyle and dietary changes.

Prior to the first democratic elections in 1994 the South African policy and institutional environment was one driven by national objectives, including military needs, food security and energy self-sufficiency. Post-1994, the development of science, technology and innovation policy in South Africa has generally followed a similar path to that of most OECD countries in terms of a 'National System of Innovation' (NSI). Such policies are aimed at moving South Africa from resource dependence to an economy relying on the intellectual capital of its people – in other words to progress to an innovative developing country. As advances in health are dependent on innovation the following Table 1 indicates the important policies, legislation and strategy documents relating to innovation and health in SA.

Table 1. Policies, Legislation and Strategies

Science ,Technology & Innovation		Health	
1996	White Paper on Science and Technology, National System of Innovation	1994	Essential National Health Research (ENHR) strategy promoting an integrated, multidisciplinary approach to focus health research on country-relevant issues
2001	National Biotechnology Strategy	1997	White Paper on the Transformation of the Health Systems in South Africa - universal and free access to comprehensive health care
2002	National Research and Development Strategy	2001	Health Research Policy in South Africa
2004	SA Biodiversity Act Chapter 6: Bio-prospecting, Access and Benefit-Sharing	2003	National Health Act
2006	R&D tax incentive system	2007-2011	Draft Tuberculosis Strategic Plan for South Africa
2007	10-year National Innovation Plan	2007-2011	HIV and AIDS and STI Strategic Plan for South Africa
2008	Technology Innovation Agency Act		
2008	IPR from Publicly Financed Research Act		

In particular the IPR act of 2008 (the SA 'Bayh-Dole Act') makes provision for intellectual property emanating from publicly financed research and development to be identified, protected, utilised and commercialised for the benefit of the people of South Africa, whether it be for social, economic or any other benefit.

The South African Medical Research Council

The MRC is South Africa's Statutory Health Research Council and, as such, funds and conducts research into pressing health issues in the country. The MRC has a strong scientific base, and supports a total of 41 intramural and extramural research units. Extramural units are situated at the major universities in the country. According to the MRC Act (Act 51 of 1991), 'the objects of the MRC are, through research, development and technology transfer, to promote the improvement of the health and quality of life of the population of the Republic.' The MRC has competence in a variety of health research areas and undertakes all of the broad disciplines of human health research from laboratory to clinical, public health, policy and implementation.

The MRC is funded through a baseline grant from government (through the National Department of Health) as well as through external contracts. Approximately half of the MRC budget of about $70 million is from external income and most of the research activities of the MRC take place with operating funds generated from competitive contracts and grants. The MRC is the most successful health research institution on the African continent in terms of its success at winning competitive international grants from some of the world's most prestigious agencies.

Innovation and technology transfer are key activities of the MRC in order to produce novel products such as drugs, vaccines, biologicals, natural medicines, medical devices and processes. They also engender economic growth and development through growing a nascent South African biotechnology and pharmaceutical industry, creating skilled jobs and bringing in foreign exchange to the country. Intellectual property management and technology transfer at the MRC are the responsibility of the MRC Innovation Centre.

Translational Research and Next Generation Best Practise

As mentioned above revolutionary technologies and evolutionary practices are driving medicine towards personalised healthcare. Revolutionary technologies are primarily related to the rapid advances in micro-electronics over the last five decades that have led to the most powerful, globally accessible tool ever invented, namely the internet.

Probably the two most important contributors to this phenomenal tool are Leonard Kleinrock and Tim Berners-Lee. Kleinrock developed the theory of packet switching (1962) and hierarchical routing (1970) which are the basis of the modern internet, while Berners-Lee created the World Wide Web (www) in 1989 based on HTTP (hypertext transfer protocol).

The same micro-electronic explosion, combined with rapid advances in biology led to the automated systems that assisted in the decoding of the human genome by the two teams lead by Craig Venter (Celera Genomics) and Francis Collins (NIH) in 2003. This biological explosion also has it roots in a similar decade (1953) when Crick and Watson discovered the so-called 'secret of life', namely the double helical structure of DNA.

The former chairman and co-founder of Intel corporation, Gordon Moore indirectly forecast these quantum advances with his prediction in 1965, that the number of transistors (hence processing power) that can be squeezed onto a silicon chip of a given size will double every 18–24 months. Knowledge is now also considered to follow Moore's Law, as it has become known, and is also reckoned to double every 18–24 months.

Within the context of health care these revolutionary technologies and evolutionary practices have lead to the emergence of digital medicine as a disruptive innovation challenging existing paradigms but promising huge benefit to patient care. This is evidenced by the fact that electronic patient records (EPRs) have already migrated from technological novelty to clinical necessity. Furthermore, building on the foundations of health informatics (1950's–1980's), digital medicine is currently expanding in several directions referred to as ehealth/telehealth/telecare/telemedicine/mhealth, all integrating ICT with diagnostics and care delivery, increasing access to care, promising enhanced quality of patient care, cost-efficiency and improving consumer access of relevant and timeous personalized health informtion.

We now postulate four generally applicable rules that are driving changes in the emerging field of digital medicine.

- All knowledge that can be digitized, will be
- All useful applications that can be web-enabled, will be
- All useful technologies that can operate on mobile / wireless devices, will be
- All useful proprietary software will lead to open source alternatives.

In (figure 1) below the progression of medical practice from symptomatic to evidence based medicine and integrated patient care is illustrated. The next generation, best practice progression to P4 medicine will by necessity include personal risk assessment incorporating clinical and genetic risk (family history, personal history and pathology, environmental factors including diet and exercise, biomarkers and genetic testing), expert systems and pre-symptomatic interventions. Together with this, will be the necessity to use ICT tools to generate and populate EPRs enabling easy, secure and remote access to comprehensive patient clinical information, combined with automated expert systems. In both these regards the SA MRC has spun-out two successful and relevant companies based on translational research outputs. These two entities are described below.

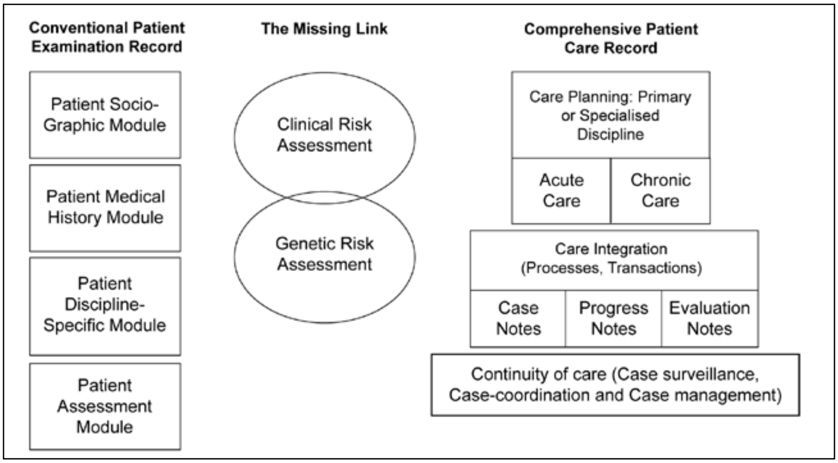

Figure 1. Next Generation, Best Practice Approach to Integrated Patient Care

Open Innovation and Translational Medicine at the MRC

The cultural mismatch between universities, research councils and industry has contributed largely to the low number of success stories at turning innovations from academic research into commercial opportunities. The performance evaluation system of university and MRC researchers that requires them to publish regularly in peer-reviewed academic journals places discoveries in the public domain, making them unattractive to investors and possible industry partners. While research is valued, innovation is mostly considered radical and disruptive and therefore these two fields largely remain independent entities

In countries such as South Africa with its combined burdens of poverty and disease, the research world is required to change. Medical scientists are expected to produce insights and innovations that have the potential to improve quality of life. A balance between research excellence and commercialisation is encouraged, and legislation (IPR Act) now requires that researchers must disclose potential intellectual property to the technology transfer office of their institution. Although commercialisation of research might seem in conflict with the purist ideals of academia, the potential to save lives and bring new techniques or tools to the marketplace would be lost without it. Basic research, however, should continue as it often gives rise to discoveries that can lead to major paradigm shifts and unimagined avenues along which more applied research can take place.

Completion of the sequencing of the human genome in 2003 led to the expectation that genomic information will lead to better medical diagnosis and treatment. This astonishing scientific feat further created the expectation that medicine could now be personalized, in that treatments would be tailored to an individual's genetic make-up. However, the discovery that the number of genes in the human genome (approximately 20k) is far less than expected has important implications. It means that the one-gene-one-disease association forming the basis of human genetics in the past is the exception rather than the rule. The human body is a complex dynamic system with multiple interacting networks. The present understanding is that only a relatively small subset of genes/proteins- of the order of hundreds- is involved in a large number of vital biochemical pathways while the majority of genes/proteins have a far less dramatic influence on health. Therefore, in this critical sub-set, the elucidation and understanding of the gene structure and mechanisms that drive the disease process is imperative when applying molecular genetics to personalized health care. To help apply this understanding and knowledge to medical practise the company Gknowmix (Pty) Ltd (www.gknowmix.com) has been spun-out.

Gknowmix is an open innovation company predicated on the fact that genetic knowledge is continuously being generated by geneticists and scientists around the world. A secure, web-based, genetic knowledge integration platform uniquely combines the multiple clinical and genetic risk variables of a patient to yield a comprehensive report through its logic/expert system. This expert system (or logic engine) requires the knowledge of scientists working on a particular gene/gene family and the associated gene-disease implications, and to incorporate this knowledge into the expert system. Consequently, through such contributions, scientists can become an independent, yet integral part of the company and be duely rewarded.

A number of disipline-specific tests (cardiovascular, wellness, cancer, etc) are already available thereby bridging the gap between the bench and the bedside. Clinicians can now request genetic counselling and testing services online for application in routine clinical practice without the need for a degree in genetics.

In addition, EPRs enable the integration of clinical and non-clinical medical disciplines with clinical diagnostic services, pathology tests, molecular genetic testing and clinical risk management into what is currently described as advanced health care services or digital medicine ¬-medicine practiced on the basis of predictive, preventative, personalized and participatory care. P4 medicine promises huge patient benefits and health care cost savings.

For this reason it was not surprising to hear President Barack Obama's pre-election statement on January 8, 2009;

'To improve the quality of our health care while lowering its cost, we will make the immediate investments necessary to ensure that within five years, all of America's medical records are computerized. This will cut waste, eliminate red tape, and reduce the need to repeat expensive medical tests. But it just won't save billions of dollars and thousands of jobs – it will save lives by reducing the deadly but preventable medical errors that pervade our health care system.'

In this context Jembi Health Systems (www.jembi.org) has been spun-out from the MRC.

Jembi is a non-profit company and non-governmental organization registered in South Africa, developing eHealth and health information systems for low resource settings. Jembi works in a number of countries in sub-Saharan Africa and also has collaborations in Latin America and south-east Asia in addition to developed countries such as the USA and Canada.

Jembi uses several open technologies, such as open enterprise architecture, open standards, open source software and open innovation. An open enterprise architecture framework is used to promote the use of open standards and facilitate access to core services and technologies that promote interoperability between health information systems. This is commonly applied at the level of a country and is used to harmonise the work of individual implementers to improve efficiency and efficacy of healthcare services. Open source software is used to promote access to low cost computer applications and improve capacity development by making source code easily accessible such that it can be adopted and modified in-country. Open innovation refers to innovative ways of combining open technologies in non-profit and for-profit organizations that can simultaneously satisfy the demands for low cost health information systems, and address wider issues such as wealth creation and poverty alleviation

Conclusion

Revolutionary technologies and evolutionary practises are reshaping global medicine and moving it from a symptomatic, disease focused field to one based on personal clinical and genetic risk assessments (family history, personal history and pathology, environmental factors including diet and exercise, biomarkers and genetic testing), expert systems and pre-symptomatic interventions. Combined with this is the necessity to use ICT tools to generate and populate EPRs enabling easy, secure and remote access to comprehensive patient clinical information incorporating automated expert systems. Digital or P4 medicine promises to be far more efficient and efffective than existing practise and also promises huge benefits for the patient. In this endeavour the SA MRC is playing its part in converting translational research into medical practise through spin-out entities such as Gknowmix and Jembi.

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THE CHALLENGE FOR GENOMICS AND MOLECULAR BIOLOGY

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China's Great Leap in Genomics

Yang Huanming

The recent progresses in biotechnology have made it even more obvious that life sciences would have significant impact on every respect of our life and society in the 21st Century. It is also widely accepted that sequencing of an organism is the basis and beginning for any further biological studies on it. BGI (formerly Beijing Genomics Institute) has recently completed four projects on the human genome, including the first Asian Genome, Human Pan-genome, Human Metagenomes and Human Ancient Genome Projects, as well as another five sequencing and analysis projects under the umbrella of the 'Tree of Life'. Genomics, together with animal cloning, SC & iPS, GM or genome transplantation, and synthetic biology, will greatly change the world in the Century of Biology.

A Century of Biology

The Human Genome Project (HGP) was one of the most important scientific projects in the 20th century and its completion has, in a sense, cultivated a new century, a 'Century of Biology'. Recent progress in biotechnology, such as iPS and stem cell research, animal cloning and bio-plants, synthetic biology and many others, have made it even more obvious that life sciences would have significant impact on every respect of our life and society in the 21st Century. These findings are just a prelude to what's shaping up as a true conceptual and technological revolution. Just as physics shook the world in the 20th century, it is now clear that the life sciences will shake up the world in the 21st century.

There are both opportunities and challenges ahead. How to work together, take actions, seize opportunities, and rise to the challenges so as to make the 21st century better for all.

EAGLES (European Actions on Global Life Sciences), which was founded to raise the banner of Science and Humanity, is serving as a platform for achieving this dialogue between scientists from the developing countries and European politicians, policy makers, members of the media and other leaders of public opinion.

As a research institution in the developing part of the world, BGI has been actively participating in the discussion on what are called HELCESS issues (Humanitarian, Ethical, Legal, Cultural, Economic, Safety/Security and Social issues) in the life sciences.

Two Pillars of Genomics

BGI, a flagship genomics institute in China for a decade now, believes that genomics is built on two pillars: biology and information sciences. As a result BGI has built powerful capacity in both sequencing and computing. The sequencing platform at BGI has a daily capacity of more than 120 Gb with new-generation sequencers, mainly Illumina-Solexa and ABI-SOLiD. BGI is also equipped with supercomputers. BGI's bioinformatics department has more than 500 young programmers and has developed most, if not all, of the software or programs for the new-generation sequencers.

Four Projects in Genomics

BGI, with its significantly expanded capacity of both sequencing and computing, has recently completed four projects in human genomics:

The First Asian Genome

'The diploid genome sequence of an Asian individual' was published in *Nature* in November, 2008, with all the data available. Our sequence data and analyses demonstrate the potential usefulness of next-generation sequencing technologies for personal genomics and mass-producing human genome sequences. Geneticist James Lupski (*Science*, 2008) of Baylor College of Medicine said that 'the methods are extremely powerful. Reading these papers, I think the personal genomes field is moving even faster than I anticipated.'

The Year 2008 also saw the initiation of the International 1,000 Genomes Projects and a project to sequence the genomes of at least 100 Chinese individuals at the BGI-Shenzhen. The goal of these efforts is not, as it was for the Human Genome Project, to sequence the genomes of a few people to build a single reference human genome, but rather to sequence very many people to build a detailed resource of genomic variation, including single-nucleotide polymorphisms (SNPs) and structural variations.

Human Pan-Genome

The paper entitled 'Building the sequence map of the human pan-genome' appeared in *Nature Biotechnology* in December 2009. This is one of the most important discoveries of the human genome in that year. In this research, BGI researchers and their collaborators estimated that a complete human pan-genome would contain ~19-40 Mb of novel sequence not present in the extant reference genome. The extensive amount of novel sequence contributing to the genetic variation of the pan-genome indicates the importance of using complete genome sequencing and de novo assembly.

Human Metagenomes

The cover story of *Nature* on 4 March 2010, entitled 'A human gut microbial gene catalogue established by metagenomic sequencing', aimed to understand the impact of gut microbes on human health and well-being, which is crucial to assess their genetic potential. BGI researchers and their collaborators defined and described at least 2000 bacterial specials and approximately 3 millions ORFs in the human gut microbes, presenting the first comprehensive catalogue of gut microbes inside human body.

Human Ancient Genome

In another cover story in *Nature* (March, 2010), 'Ancient human genome sequence of an extinct Palaeo-Eskimo', BGI researchers and their collaborators reported the genome sequence of an ancient human. Obtained from 4,000-year-old permafrost-preserved hair, around 80% of the human genome sequence represents a male individual from the first known culture to settle in Greenland. It also indicates the possibility to sequence trace amount of partially degraded DNA samples.

Five Other Projects in the Tree of Life

The Human Genome Project ushered in a new era of turning Darwin's language into ATCG/sequence. The 'Tree of Life' Sequencing Projects are aimed at getting more knowledge of evolution and genomes, getting gene resources for breeding & man-made life. To get its genome sequence is only the beginning of further studies of this organism. BGI and its collaborators have sequenced and preliminarily analyzed several genomes with all the data on line, including the Giant Panda Genome (*Nature*, 2010), 40 Silkworm Genomes (*Science*, 2009), and the Cucumber Genome (*Nature Genetics*, 2009).

BGI plans to sequence the genomes of 1,000 important plant and animal reference species over the next few years as part of a new project that will solicit proposals from the scientific community. An international committee organized by BGI will select the species to be sequenced from proposals by researchers, based on the importance of the species, the applicant's financial resources, the project's scientific strength, and the experimental design.

Researchers from BGI, the University of South Florida, and the University of Maryland plan to collaborate on a symbiont genome project as part of BGI's 1,000 Plant and Animal Reference Genomes Project. The team will sequence the genomes of the sea slug, *Elysia chlorotica*, and its algal food source, *Vaucheria litorea*.

There are several important *De novo* sequencing projects by BGI, including polar bear in the north pole, penguin in the south pole, and Tibetan antelope on the world roof, as well as Potato Genome Project. The purpose of '10000 Microbial Genome Project' is to build a microbial genome encyclopedia. BGI-Shenzhen will lead a project with its collaborators that will begin development of a genomic encyclopedia of microbes in China. The microbes the project plans to study include archea, bacteria, fungi, algae, and viruses from conventional environments such as soil, air, and water, and from extreme environments such as glaciers, deep ocean hot springs, and outer space.

Conclusion

As a relative latecomer to the modern life sciences, the growth of BGI is deeply rooted in Chinese tradition and culture, for example: 1) Foresight:

'Success could not be made without foresight, failure from no prediction'. 2) Persistence: 'Winners are only those with persistence'. 3) Learning: 'Among those three passing by, at least one is qualified to be your teacher'. 4) Confidence: 'The later comers always do a better job because of the pioneers ahead'. 5) Collaboration: 'Nobody could be a hero without three partners'. 6) Appreciation: 'When you drink sweet water, never forget those helped dig the well'.

Genomics cannot be done alone. BGI calls for international collaboration and science for better life for all in the 21^{th} century.

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Evolution of Human-Microbe Interplay: Challenges and Opportunities

Adel Mahmoud

Establishment of the germ theory approximately two centuries ago formed the current understanding of human-microbe interplay. It resulted in a focus on the pathological aspects of the relationship and completely neglected the multifaceted features of the interplay between humans and the microbial world. It also led to the articulation of the 'War Metaphor', which in spite of some successes resulted in the serious development of resistance in the target organisms. In recent years, several new approaches including evolutionary biological studies, genomics and metabolomics of human microbiota are paving the way to a more comprehensive understanding of human-microbe interplay.

Central to these findings is the appreciation that humans and the more abundant microbes are coinhabitants of this globe and that their interaction is much more complex than simply a pathological dwelling. The microbial worlds are engaged in multifaceted relationship with humans or other animal hosts spanning the spectrum from commensalism, symbiosis, and mutualism and only in a limited sense it results in disease. This understanding will determine what results in persistence of some microbes in their human host with no disease sequalae and what is the basis of virulence and pathological consequences. Equally significant is appreciating the genomics and metabolomics of microorganisms and utilize this understanding for the development of new preventive and therapeutic tools. We trace the steps taken to appreciate the etiology of cervical cancer from epidemiologic observations to extensive clinical studies followed by detailed molecular evaluations.

This effort focused on human papillomavirus as the main etiologic agent. The effort then proceeded to sequencing the viral genome, examining its proteome and determining the function of each of these viral products. This was a tremendous scientific effort that led to the ultimate development of significantly effective human papillomavirus vaccines

Introduction

The conceptualization of 'Germ Theory' by Louis Pasteur and Robert Koch is a landmark in understanding one aspect of the interplay between humans and microbes. The 'Germ Theory' also provided the first scientific evidence for the concept of etiology of diseases as a consequence to the introduction of microorganisms in humans or experimental animals. It has to be recognized however that the concept of contagion was advanced as the process by which some diseases such as syphilis were acquired almost two hundred years earlier than the formulation of the 'Germ theory'. This was achieved based on astute clinical observations since the existence of microorganisms was not appreciated until the first primitive microscope was developed several decades later and viruses were only detected with electron microscopy in the early 20th Century. Even the description of vaccination in 1796 by Edward Jenner was not based on identifying an etiologic agent rather; it was his clinical observations and the ability to perform an exposure study that would not be allowed today.

The most significant impact of the 'Germ Theory' was the recognition and establishment of specific microbes as the etiologic agents of specific diseases of humans or experimental animals such as tuberculosis, cholera, plague and others. It also provided the concept of treating infectious disease by either removing the infectious agent or preventing its access to their host. Vaccination and antimicrobial agents became the two most frequently used approaches respectively for prevention or treatment. The remarkable discovery of penicillin and many other antibiotics established our approach to microorganisms that cause human or animal diseases for almost a Century but at a cost that is threatening such an approach.

A major consequence of 'Germ theory' is a firm establishment of what Joshua Lederberg (Lederberg, 2000) coined as the 'War Metaphor'. It reflects that the relationship between humans and microbes is a struggle 'we vs. them'. Such limited understanding of the relationship resulted in neglecting or under appreciation of the multifaceted aspects of the interplay as we explore below. More significant for human health, is that the ultimate outcome of the war metaphor was the development of the massive spread of antimicrobial resistance. The challenge, therefore, is to reexamine all aspects of human-microbe interplay in an attempt to provide a more comprehensive appreciation of its multiple aspects and to reverse or minimize its pathological consequences by alternative approaches.

Evolutionary Biology of Human-Microbe Interplay

Humans and microbes have been coinhabitants of this globe for millions of years and their interactions have evolved in multiple ways from structural to functional as well as antagonistic relationships. The earliest evidence for structural interaction relate to the acquisition of all eukaryotic cells of bacterial mitochondria which are essential for their survival in a toxic atmosphere. Mitochondria are believed to have originated from α-proteobacterial endosymbionts that were integrated into host metabolism (Andersson, et al., 1998). The structure of the different components of mitochondria in humans and many animal species resemble to a great extent bacterial mitochondria. Furthermore, there are close similarities between the metabolic pathways of human mitochondria and those of some bacterial and rickettsial organisms which strongly support common ancestory.

Another structural aspect of human-microbial interaction became evident following the sequence of human genome. It turned out that a small but significant proportion of human genome is of retroviral origin. These human endogenous retroviral elements are evidence for infection of primordial cells and integration and propagation of these sequences in human genome. Evidence is currently being accumulated that some of these sequences have open reading frames that upon expression in vitro are capable of forming complete virions (Kurth, et al., 2010)). Table 1 summarizes some of the currently available evidence for a functional or pathogenic role for these retroviral elements (Kurth, et al., 2010). The full extent of the functions and relevance of human endogenous retroviruses is a subject of current intensive investigation.

Table 1. Representative HEFV families and their detrimental or beneficial effect.

HERV Family	Copy number1	Suspected effect	Refs2
Gammaretroviral (Class I)			
HERV-E	250 (1000)	Opitz syndrome	17
HERV-W	40 (1100)	Placenta formation	60
HERV-FRD	50 (2000)	Placenta formation	57
HERV-H	1000 (1000)	Gene expression	42
Betaretroviral (Class II)			
HERV-K (HML-2)	60 (2500)	Carcinogenesis	81
Spumaviral (Class III)			
HERV-L	580 (6000)	Fv-1 restriction in mice	43

1) Copy number of solo LTRs is given in parentheses. 2) For additional details and examples see (Bannert, et al., 2004). This table was taken from Bannert & Kuth, 2010 with permission.

Human Microbiota

We are at an early stage of examining the microbial communities that share the human body either in internal organs such as the large intestine, buccal cavity or exist on the skin surface. It is now being appreciated that the human large intestine is inhabited by many bacterial species that predominantly belong to five bacterial phyla. The total genome of these organisms exceeds several times the size of human genome. Intestinal microbiome play an important nutritional and immunologic functions that are necessary for human survival and development (Turnbaugh, et al., 2007). This mutual relationship is the most dominant feature of the intestinal microbiome and only in limited circumstances additional organisms may invade the human intestine and cause disease. Knowledge is currently accumulating of other microbial communities in humans as well as an early attempt to develop similar data base for viruses that live in or on our bodies. The total picture evolving is that humans are actually 'Super Organisms' made of what we recognize as human genome in addition to multitudes of microbial genomes (Lederberg, 2000).

The spectrum of relationships between humans and microbes spans a wide variety of conditions ranging from commensalism to mutualism and under certain circumstances it results in pathogenesis (Dethlefsen, et al., 2007). How this relationship is regulated is currently poorly understood. In some instances infection, meaning introduction of a microbial organism in humans will lead to persistence such as in several viral, bacterial or protozoan infections and very little or no evidence of causing harm in the host. In other circumstances infection progresses to disease causation. One of the most significant challenges of understanding human-microbe interplay is to determine the mechanisms regulating the outcome of this interaction.

The challenge of Human-Microbial Interplay

Appreciation of the multiple facets of human-microbe interplay is a significant step towards changing the 'war metaphor'. The need is urgent to examine evolutionary as well as molecular basis of this relationship and to attempt managing its outcome with the least costly impact on the human host. Fundamental to this approach are three scientific pursuits that can shape a better understanding of human-microbe interplay.

First, a new scientifically rooted appreciation of the role of evolutionary sciences and evolutionary biology in determining the outcome of human-microbe interaction. For example, it is currently recognized that over half of human infectious agents exist in nature in animal populations. These zoonotic infections cross species under circumstances that are poorly understood. Study of zoonotic dynamics and its components including whether they relate to prevalence of infection in animal reservoirs, the contact between these reservoirs and humans and finally the probability of infection will be necessary. These factors can be incorporated into dynamical models that should help understand the process and devise appropriate counter measures (Lloyd-Smith, et al., 2009).

Second, a major effort should be designed to explore the fundamental molecular structure and organization of microbial organisms. Many human pathogen genomes have already been sequenced. It is the first step towards understanding the regulation of their interaction with humans. Central to these efforts is the ability to dissect microbial proteome and to determine the function of its products as well as examining their interaction with host molecules (metabolomic investigations).

Third, taking a significant quantitative step towards appreciation of the host relevant immune responses for development of disease or induction of protection. The transformation of the science of immunology from qualitative into quantitative pursuits and identifying the components and regulation of how host deals with extracellular or intracellular pathogens or those presenting inside infected host cells will pave the way to appreciation of the effector molecules of each mechanism.

Discovery and Development of HPV Vaccine

We will use the discovery and development of effective vaccines against human papillomavirus infection as an illustration of the power of applying the three principles articulated above for guiding a new appreciation of human-microbe interplay and utilizing this appreciation to develop effective prevention tools. Identification of the causal relationship of human papillomavirus infection and persistence to cervical carcinoma was a remarkable achievement that was awarded the Nobel Prize in 2008 (zur Hausen, 2009). The discovery was based on meticulous investigation and clinical as well as epidemiologic observations. Definitive proof came from pathological and molecular examination of cervical cancer tissue samples. HPV viral DNA was almost regularly demonstrated integrated in the genome of these samples. This association resulted into intensive molecular studies of HPV, its genome and proteome. Viral DNA sequence demonstrated a double stranded structure with several open reading frames. All protein products were isolated and characterized. It also was possible to evaluate the function of each protein and led to identification of the oncogenic properties of two of the early viral proteins and relating their role to cancer association of certain subtypes of HPV. Further evaluations of viral proteome identified other cell cycle regulatory molecules that are involved in viral internal functions. As the effort to study most viral proteins progressed, it was reported in the early 1990's that cloning and expression of the capsid protein L1 of HPV resulted in a self assembled structure (Virus-Like Particle) made of only one protein (L1) and folded as whole virus (Zhou, et al., 1991). This observation was reminiscent of the self assembly of the cloned and expressed Hepatitis B virus which formed the basis of the currently available and widely used Hepatitis B vaccine. By the middle of the first decade of the 21st Century, two highly effective HOV vaccines are being deployed in many countries.

The translation of a research finding as in this case, the self assembly of a viral protein into VLP's, is only the first step towards developing an effective vaccine. Human papillomviruses are a family of many members, some are oncogenic, others are the causative organisms of genital warts and still many others are non-pathogenic to humans and result in self clearing infections. To develop effective vaccines, it was important as a first step to determine a product profile that gives maximum benefit. The two available vaccines contain VLP's for HPV types 16 and 18 that are responsible for approximately 70% of cervical cancer cases. In addition, one of these two vaccines contains VLP's for types 6 and 11 which are responsible for approximately 90% of genital warts cases (Brown, et al., 2009). The developmental process was therefore, designed to produce either two or four separate populations of VLP's and optimize their inclusion in one preparation to minimize antigenic competition and to induce an effective, protective and sustained immune responses. To maximize the impact of these vaccines, it was essential to disassemble the VLP's and reassemble them to produce uniformly sized and effective preparations (Mach, et al., 2006).

Conclusions

Human-microbe interplay has to be viewed in an evolutionary perspective that recognizes the multifaceted aspects of this relationship. In addition, significant advances in appreciation the complexity and regulation of the interaction will rest on a lot more basic scientific investigations of the molecular structures and organization of microbial organisms and a more quantitative appreciation of host immune and protective responses. Enhanced recognition of the functional role of human microbiota and the mechanistic features of commensalism and mutualism may pave the way to change our approach to microbes from the 'war metaphor' towards a more intelligent design for 'our wit vs. their genes' (Mahmoud, et al., 1983).

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Alternative Splice Variants as a New Class of Cancer Biomarker Candidates

Gilbert S. Omenn

The genetic revolution unleashed by the Human Genome Project requires integration of extensive analyses of genes, proteins, and regulatory mechanisms in cells, organs, and people. One of the surprising lessons from the human genome is the modest total number of protein-coding genes. It turns out that alternative splicing plays an important role in generating protein diversity without increasing genome size. We have designed a discovery pipeline for alternative splice variant proteins from tandem mass spectrometry datasets. We have demonstrated its capacity to identify both known and novel splice variants differentially expressed in cancers. Splice variants are a new class of cancer biomarker candidates

Introduction

The 21st century began with the near-completion of the Human Genome Project, a remarkable global initiative capitalizing on dramatic advances in instrumentation, chemical technologies, and databases. The project was based on the realization that biology is an information science. During the weekend of 15–16 February 2001, the journals *Nature* and *Science* published entire issues dedicated to presenting the human genome sequence and associated analyses from the public sector, led by Francis Collins of the U.S. National Institutes of Health, and the private sector, led by Craig Venter of Celera, Inc., respectively. The key technologies that enabled the whole project were miniaturized methods for DNA sequencing and DNA synthesis and for protein sequencing and protein synthesis, created under the leadership of Leroy Hood, then at the California Institute of Technology and his colleagues at Applied Biosystems Inc. The research community is actively filling in details of the genome sequence and learning more and more about the regulation of gene expression in health and disease.

One major surprise from the human genome was the number of protein-coding genes. Early predictions ranged from 50,000 to 100,000 or more; instead, it turns out that the actual number is much closer to 20,000, with a current best estimate of 20,344 genes in the GenBank and SwissProt/UniProt databases. One way that the human genome appears to have achieved genetic variability and expanded genomic information transfer is by utilizing alternative splicing through multiple mechanisms, thereby generating multiple gene products from the two strands and various reading frames involving a given gene.

Fully understanding the biological significance of the genome sequence requires what is called 'functional genomics'—knowledge about the regulation of gene expression, protein production from the protein-coding genes that utilize about 1.5% of the genome sequence, and extensive modifications of proteins that affect their structure and function. Proteins are the main effector molecules of the cell—structural components, oxygen—carrying hemoglobin, enzymes, receptors, hormones, regulatory proteins, and many other classes. In fact, just six days after the *Nature* and *Science* issues appeared, the *Financial Times* of London on 21 February 2001 had a lead story entitled 'Searching for the Real Stuff of Life', with a cartoon that showed DNA off-stage in the shadows and a lively globular protein dancing under the spotlight on-stage. The companion article called the field of 'proteomics' and its goal of deciphering the human protein set 'Biotech's Next Holy Grail'.

Functional genomics comprises multiple layers of molecules and their interactions, as shown in (Figure 1). A whole new set of terms referring to global analyses of all genes, proteins, and other molecular features has emerged. These terms include, besides genomics for all the genes, transcriptomics for gene expression in the form of messenger RNAs, proteomics for all the proteins and their networks, metabolomics for large numbers of metabolites and their pathways, epigenomics for the methylation and other modifications of DNA and chromosomal histone proteins, and regulomics for the mediation by proteins, microRNAs, and other molecules of gene and protein expression in response to the actions of environmental chemical, physical, and infectious agents and individual and social behaviors..

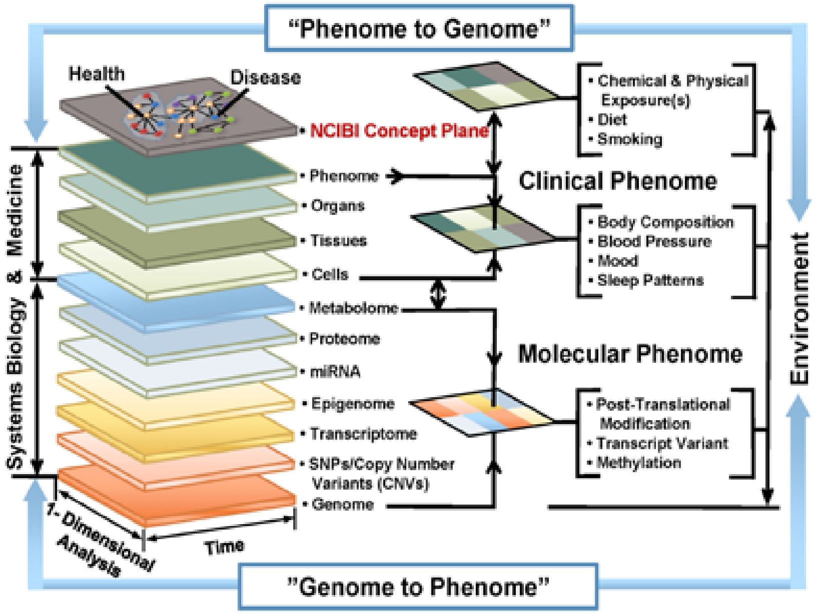

Figure 1. Schema for functional genomics, linking genotype to phenotype, or genome to phenome, through multiple molecular layers of analysis, anatomical and physiological features, external exposures, and clinical and laboratory measurements.

Aims for Proteomics of Cancers

A major goal of proteomics is better understanding the roles of the many classes of proteins in the initiation, progression, and metastasis of cancers. The experimental approaches start with profiling proteins in tumor specimens, compared with normal tissue of the same organ, and profiling proteins circulating in the blood. This phase is called 'biomarker discovery research'. The aims are: (1) to discover and validate protein biomarkers in tumor specimens for diagnosis and stratification of patients, for prognosis without therapy or with particular therapies, and for clues to biomarkers that could be detected in the circulation; (2) discover and validate biomarkers in the plasma (or serum) for earlier diagnosis and for prediction and monitoring of responses to therapy and emergence of recurrent tumor after successful treatment.

For many years, investigators have performed biomarker discovery research starting with plasma specimens from cancer patients and controls. This approach has proved quite challenging, due to multiple specific barriers: human cancers are highly heterogeneous, from patient to patient, as well as at the cellular and genetic level within the tumor itself. Tumor proteins are in low abundance even within the tumor at early stages of cancers. Tumor proteins that are released into the extracellular fluid and the circulation are greatly diluted in concentration in the 4-5 liters of blood, making detection much more difficult. Plasma is an extraordinarily complex specimen dominated by albumin and other very high abundance proteins; and knowledge of the plasma proteome is still limited, with about 2,000 proteins confidently identified in the Human Plasma PeptideAtlas (www.peptideatlas.org). Thus, it is common now to start with tumor specimens, using microarrays or next-generation sequencing for evidence of carcinogenic pathways and mechanism, then track corresponding proteins from the tumor to the plasma. Sometimes auto-antibodies can be detected that recognize these tumor protein antigens; antibody production is a very useful biological amplification of the tumor antigen signal, often by 100 to 1000 fold. Once good biomarker candidates are identified and confirmed, specific assays can be created for selective reaction monitoring (SRM) or multiple reaction monitoring (MRM), which generates quantitative results for the protein levels in specimens compared.

Alternative Splicing: A New Class of Biomarker Candidates

In recent years, there has been growing recognition that alternative splicing is a much more common feature of genomic information transfer and gene and protein expression than previously suspected. In fact, alternative splicing accounts for at least part of the explanation of how the human genome can be a blueprint for so many complex functions with only about 20,000 protein-coding genes. Splicing generates multiple different protein products from a single 'gene'. Thus, splicing generates protein diversity without increasing genome size. As we will show below, there are multiple mechanisms for splicing—involving 5' and 3' start sites, mutually exclusive exons, cassette exons, intron retention, alternative promoters, and alternative polyadenylation. The rapid advances in tandem mass spectrometry instrumentation enables confident identification of peptides from proteins coded by mRNA transcript sequences expressed at quite low levels.

We have created an Ensembl and ECGene-derived target database of all potential translation product sequences of >= 14 amino acids for humans and for the mouse, with 14.2 million and 10.4 million protein sequences, respectively. We search mass spectrometry spectra against the modified ECgene database using X!Tandem software and TransProteomicPipeline and the Michigan Peptide-to-Protein Integration workflows. We demonstrated its usefulness with analyses of the findings from extensive proteomic analysis of plasma samples from genetically-defined mouse models of human pancreatic cancer and of tumor specimens from a genetically-defined mouse model of human Her2/neu breast cancer, compared with normal plasma and normal breast tissue, respectively.

Identification of Splice Variant Peptides in Plasma of Mice with KRas G12D/Ink4a/Arf Deletions and Pancreatic Ductal Adenocarcinoma

Pancreatic ductal adenocarcinoma is the most lethal of human cancers, with five-year survival of less than 5 % and 31,000 deaths per year in the United States. The mutations in this mouse model were engineered by Depinho and Bardeesy to match the molecular lesions in the vast majority of human pancreatic cancers. Our integrated analysis of datasets from the Hanash Laboratory at the Fred Hutchinson Cancer Research Center in Seattle revealed 420 distinct splice isoforms, of which 92 were novel, matching no previously annotated mouse protein sequence 4. An example is shown in (Figure 2), the pi16 peptidase inhibitor.

We validated selected peptide findings by designing primers and performing qRT-PCR to demonstrate the corresponding spliced sequence in the messenger RNA for seven of the novel peptides. Isotopic labeling made it feasible to detect differential expression in many novel variants which, based on literature search, may well be involved in specific aspects of pancreatic cancer progression. One especially interesting variant involves pyruvate kinase, the critical enzyme in the metabolic switch to aerobic glycolysis in cancers, known since its report in 1929 as 'the Warburg effect'. We also examined the proteins reported by our collaborators not only in the mouse model but in patients with pancreatic cancers, and were able to identify splice variants for three of the nine proteins they proposed as potential biomarkers for pancreatic cancers in humans: lipocalin 2,

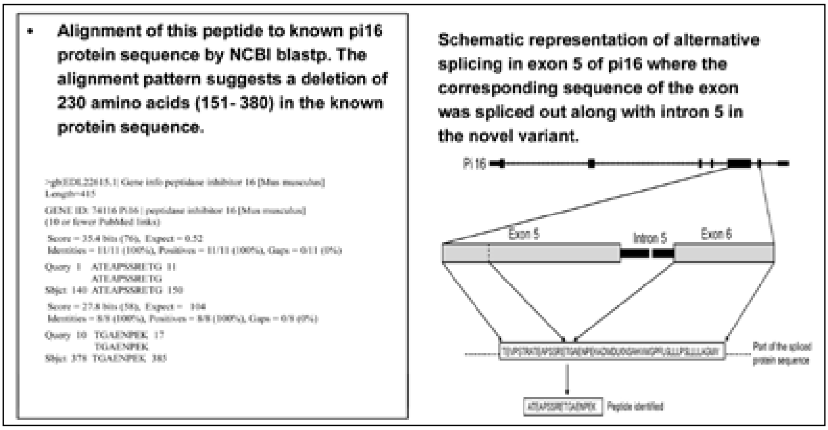

Figure 2. Schematic representation of alternative splicing in exon 5 of the peptidase inhibitor pi16 from the plasma of mice genetically-engineering to develop ductal adenocarcinoma of the pancreas. A novel variant was identified from the unique sequence ATEAPSSRETGAENPEK. Alignment of the peptide with Blastp from the National Center for Biological Information (NCBI, NIH) suggested deletion of 230 amino acids (residues 151-380) in the known protein sequence. The corresponding sequence of exon 5 (top scheme) was spliced out along with intron 5 in the novel variant, as shown in detail in the lower portion of the Figure[4].

regenerating islet-derived 3, and tumor necrosis factor receptor superfamily member 1A (tnfrsf1a). For example, based on our quantitative expression analysis, the tnfrsf1a showed two-fold increase in expression in plasma from the tumor-bearing mice compared with plasma from the wild-type mouse.

Identification of Splice Variant Peptides in Tumor Tissue of Mice with Her2/Neu Breast Cancers

Here we analyzed datasets from the proteomic analyses of Whiteaker et al., 6 in the Paulovich Laboratory at the Fred Hutchinson Cancer Research Center, available from PeptideAtlas. These specimen did not undergo isotopic labeling, instead, we used label-free spectral counting to assess quantitative differences in expression levels 5. We found a total of 608 distinct alternative splice variants, 540 known and 68 novel. Of the 15 biomarker candidates Whiteaker et al., confirmed as over-expressed in tumor lysates with quantitative MRM mass spectrometry, we found that 10 of these had splice variants in our analysis. At this point, we do not know whether these variants have differential biological activities compared with the wild-type.

Protein	Novel peptide	Mgi symbol	Sample type	Probable splicing mechanism
M14C435_25_s53_e5231_1_rf1_c1_n0|	ITFDDHKNGSCGVSYIAQEPDAP	flnb	tumor	intron retention
M19C1480_7_s383_e953_1_rf1_c1_n0|	ATETARLLPGTALAEAQSPLRRLTLTQAPPR	fth1	tumor	located in the 5'UTR region; alternate translation start site
M15C7603_11_s1181_e1415_1_rf1_c1_n0|	QTSSRPAMGGGTARWQR	gapdh1	normal	different frame; frame 2
MXC910_48_s179_e2030_1_rf0_c1_n0|	LLEELAAARPGEPALMSSSPLSKKRR	uba1	normal	novel peptide from Ensembl exon 2 and 3 junction; the currently annotated Ensembl cDNA starts from exon 3
M7C13466_20_s2_e518_1_rf2_c1_n0|	EARSLSDGGPADSVEAAK	nap1l4	tumor	exon skipping; exon 2 skipped

Figure 3. Sequences reflecting splicing from novel peptides from five proteins are presented here, two from breast tumor specimens and three from normal breast tissue in the Her2/neu mouse model. The final column presents the probable splicing mechanism at play in each situation, deduced from the sequence information. These examples represent an even greater variety of potential mechanisms for splicing in the full study. It is possible that difference mechanisms reflect different causes and are associated with different consequences for protein function. The proteins listed here are flnb, filamin B; fth1, ferritin heavy chain; gadph1, glyceraldehydes-3-phosphate dehydrogenase; uba1, ubiquitin-like modifier activating enzyme 1; and nap1l4, nucleosome assembly protein 1-like 4.

As shown in Figure 3, among the novel proteins we deduced the nature of the splicing event in many variants. We demonstrated variants that resulted from new translation start sites, new splice sites, extension or shortening of exons, deletion or switch of exons, intron retention, and translation in an alternative reading frame. In our annotations, 16 of the novel peptides found only in the tumor sample and with increased mRNA expression by PCR were highlighted because of functional motifs potentially significant in cancers. For example, there were variants of two genes—leucine-zipper-containing LZF rogdi gene and transcription factor sox7—with interesting annotations for the BRCA breast cancer gene; they have phosphopeptide motifs which interact directly with the carboxy-terminal domain of BRCA1. We intend to model interactions with BRCA1 for each of these protein domains.

Linking Protein Structures and Proteomics

Together with Yang Zhang of the University of Michigan, my colleague Rajasree Menon and I have initiated a whole new type of research linking splice sequence variants with computerized analyses to predict 3-dimensional structures of proteins and infer the functional consequences of exon swapping, insertions and deletions, and other changes due to splicing in specific wild-type and splice variant isoforms of a given protein. We have beautiful views of the direct alteration in protein conformation involving alternative use of exon 9 or exon 10 in pyruvate kinase M and even more interesting changes in distant parts of the protein molecule when ATP binding occurs. Other interesting observations are being confirmed and characterized.

Network Analysis for Proteins with Alternative Splice Variant Isoforms

We utilized GeneGo Metacore software to characterize significant biological processes. Cytoskeletal rearrangements, integrin-mediated cell adhesion, and translation initiation were foundin common among the top-ranking networks from tumor-associated splice variants. Figure 4 shows direct protein interactions displayed by Cytoscape with a plug-in from Michigan Molecular Interactions (MiMI); 177 of 460 input gene symbols are shown to be interacting.

The gene names in bold denote differentially expressed alternative splice variants. These include many of those we had already annotated as candidates for a role in the systems biology of breast cancer. Cdc42, arhgdia, and rdx are among these proteins 5. Proline-rich motifs in specific splice variants of rdx and other proteins involved in extracellular tumor microenvironment and cell motility can be contrasted with other known isoforms of these genes which do not contain these proline-rich regions. It is likely that these motifs participate in the actions of these proteins in delivering actin monomers to cellular locations where ruffles, filopodia, and microspikes are formed.

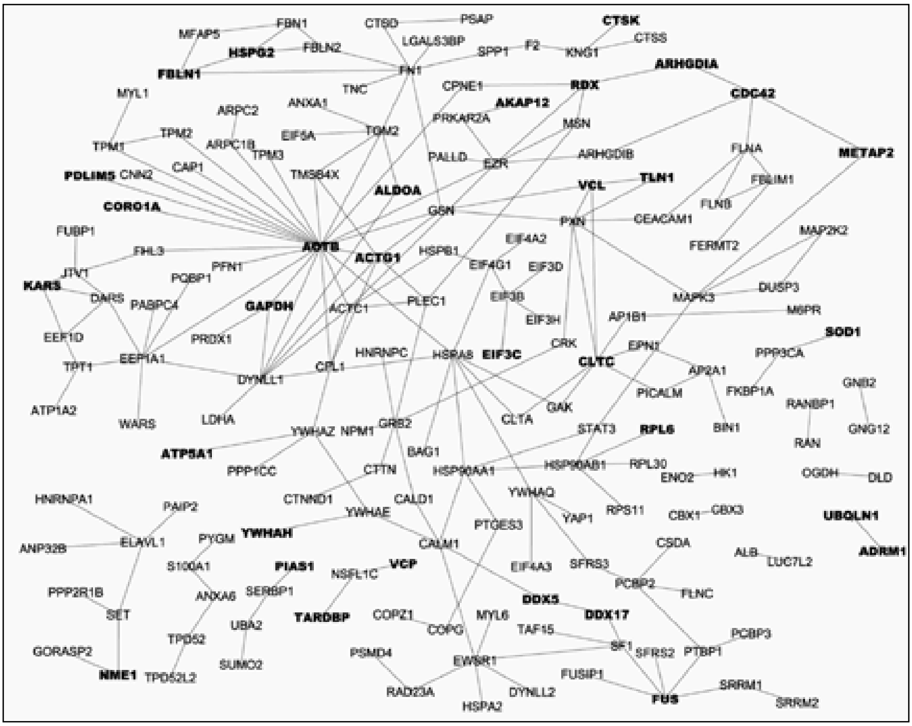

Figure 4. Protein interaction network displayed in Cytoscape with Michigan Molecular Interactions (MiMI) plug-in. The input gene list contained the alterantive splice variants found only in the tumor sample. Only direct interactions between input genes are shown. The gene symbols in bold are those were annotated in depth in the original publication. For example, note the interactions of arhgdia, rdx, cdc42, and metap2 in the upper right.

Conclusion

We are in the earliest stages of identifying and characterizing alternative splice variants for their potential roles in systems biology of cancers, including such critical features as initiation, progression, cell motility, invasiveness, and metastasis. We are comparing evidence of splicing by next-generation RNA-sequencing with evidence from mass spectrometry-based proteomics. Much further research is needed to delineate major subtypes of common cancers, link findings in mouse models to corresponding human cancers, predict likely changes in protein structures and functions, and propose and validate use of these proteins as targets for therapy and biomarkers for diagnosis, prognosis, and response to treatments.

Acknowledgements

I thank Dr Rajasree Menon and Dr Anastasia Yocum for their major contributions to this new line of proteomics research, and Drs Ronald Depinho, Nabeel Bardeesy, Samir Hanash, and Amanda Paulovich for their making extensive proteomics datasets from mouse models of human cancers available for our analyses and annotations. I acknowledge grant support from NCI/SAIC contract NO1-CO-12400/Sub-k 23XS110; Michigan MTTC GR 687; and NIH U54 DA021519 National Center for Integrative Biomedical Informatics.

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Bioinformatics and Genomics Sciences in the Middle East

Yaqoub Ashhab

Bioinformatics and genomics sciences are becoming indispensable to develop our knowledge in vital fields such as medicine, food and agriculture, and biodiversity. Unlike other science and technology disciplines, research and development in bioinformatics does not require prohibitive resources. As the accessibility of most biological databases in the public domain is no longer an issue, the Middle East region stands before a great opportunity to move from being a receiver of science and technology to being a producer and direct contributor to the development of bioscience and technology in the fields of medicine, food and agriculture, industry, and environment.

The emergence of Bioinformatics

Bioinformatics is an emerging interdisciplinary field that focuses on solving biological problems through the use of informatics, computer science and statistics. Thanks to computer and information technology power, bioinformatics has shown a remarkable capacity to manage vast amount of biological data generated by high-throughput genomics, transcriptomic and proteomic techniques. The major tasks of bioinformaticians are to develop computer-based databases and tools that can facilitate acquisition, storage, curation, retrieval and analysis of biological data.

Evolution of bioinformatics has always come as a response to the evolution in biological data acquisition. Prompted by the increase in the number of protein sequences, revealed using Sanger's protein sequencing method, Margaret Dayhoff and her coworkers at the National Biomedical Research Foundation (NBRF) established during the 1960s the first biological database, which was known as Atlas of Protein Sequence and Structure (Mount, 2004). With the development of efficient direct DNA sequencing technology during the late 1970s, the need emerged to develop nucleic acid sequences databases such as GenBank and EMBL Data Library to store the new data (Hingamp et al., 1999). Parallel to the exponential increase in sequence data, interest also increased in developing various computer-based algorithms and tools to analyze biological sequences in order to facilitate the generation of meaningful information.

Since the mid 1990s, the emergence of a wide range of high-throughput experimental approaches to study the whole genome of an organism has taken bioinformatics into new horizons to address biological questions that are otherwise unattainable using conventional methods. Bioinformatics laid the foundations of new disciplines such as genomics, transcriptomics, proteomics and metabolomics that are together necessary to develop the system biology approach, which is supposed to enable us to see the complete picture of living organisms (Campbell and Heyer, 2006).

It is clear that the blossoming of bioinformatics and genomics depended on the magnificent advancements in biomedical, biotechnological and agricultural research and acted as a catalyst to the further advancements of these fields. Bioinformatics has proven to be an indispensable tool in modern biosciences, both in research and education. In the last two decades, bioinformatics has been catalyzing many innovative discoveries in various vital fields. Therefore, countries that have decided to take a leading position in biosciences and biotechnologies have to consider bioinformatics research and education as an integral part of their science and technology strategy.

In spite of the fact that most biological databases are freely accessible and in addition to the availability of much computational biology tools and software, most developing countries including those in the Middle East are still lagging in the race to harness the full potential of bioinformatics. In this article, the major opportunities and challenges that need to be addressed by Middle Eastern countries in order to catch up with this rapidly growing and promising discipline will be discussed. Hereinafter, the Middle East refers to the traditional definition that includes Turkey, Syria, Lebanon, Palestine, Egypt, Saudi Arabia, Yemen, Oman, United Arab Emirates, Qatar, Bahrain, Kuwait, Iraq, and Iran.

Current Research Status

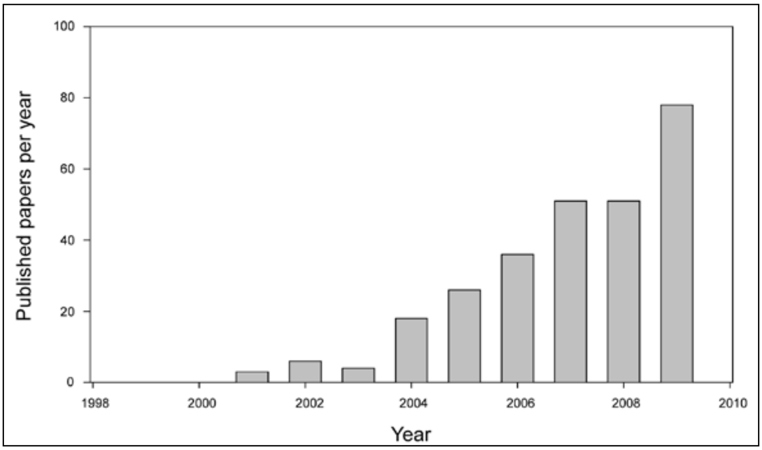

Figure 1. Bioinformatics publishing in Middle Eastern Countries

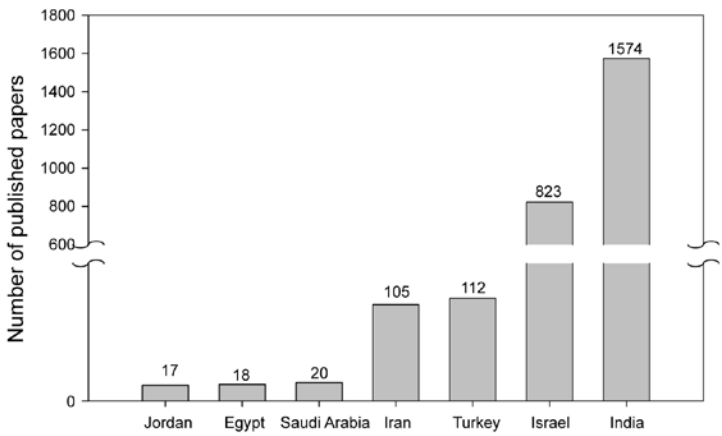

Figure 2. Bioinformatics Related Publications by Some Middle Eastern Countries. The graph shows PubMed search results (per country) of the published papers, until August 2010, that contain either of the following key words: bioinformatics, bioinformatic, computational biology, in-silico, biological databases. The searches were limited to the publications with the indicated countries as author's affiliation.

A belated interest in bioinformatics and its tools by research institutes and universities in the Middle East did not occur until after the year 2000 (Figure 1). It is actually a decade later than the emergence of this field in Israel (Nussinov, 1989). In order to assess bioinformatics research activities, PubMed.gov, which is a free bibliographical resource at the U.S. National Library of Medicine (NLM), was used. The number of publications in peer reviewed journals that were indexed by PubMed was considered as a comparative indicator for research activities in each Middle Eastern country. It is obvious that Turkey and Iran are the most active Middle Eastern countries in bioinformatics. Saudi Arabia, Egypt, and Jordan are in the second position (Figure 2). The rest of the Middle Eastern countries have very little internationally published research work in bioinformatics

A thorough analysis of the published works, reveal that most of the current research activities in this field are based on individual initiatives. However, a few institutes have integrated computational biology and bioinformatics to their strategic plans such as the Computational Bioscience Research Center at the King Abdullah University of Science and Technology in Saudi Arabia, which is a recently established center that aims at developing cutting-edge computational technologies so as to accelerate biomedical and biotechnological discoveries for the benefit of the people of Saudi Arabia and the region.

Relevance to National Strategies

It is important to recall that bioinformatics is a supportive tool and a set of technologies that are crucial to promote biomedical, biotechnological and agricultural research. We should bear in mind that development of bioinformatics alone should not be a national strategic goal per se. Therefore, Middle Eastern countries need to address their requisites to build a good bioinformatics platform in an integrative strategic context.

Development of the national bioinformatics capacity should be part of a country's strategic plan that aims at enhancing sustainable development and management of natural resources with the general mission to contribute to the well-being of society in terms of health, food, environment and economic growth.

Bioinformatics and genomics can play a key role in meeting serious health, agricultural and environmental challenges that face the region. In the health care field, genomics and bioinformatics can be instrumental in understanding and better treating genetic diseases, improving surveillance and control of infectious diseases, and designing novel diagnostic tools and vaccines. The sequencing and analysis of the genomes of indigenous plants can have significant implications on the development of crops that tolerate drought, salinity and microbial diseases. In addition, these technologies can pave the way to identify and modify microbial organisms in order to be used in wastewater management.

Establishing a successful bioinformatics and genomics framework needs the active involvement of a wide spectrum of stakeholders throughout the discussion, planning, implementation and monitoring process. Potential stakeholders include academia, software industry, pharmaceutical and diagnostics industries, agro-tech companies, government agencies, and patient advocates. Joint ventures driven by stakeholders from public and private enterprises, ensures sustainable investment in the biotechnology sector. However, we have to admit that most Middle Eastern countries, and due to cultural and political reasons, are not yet familiar to the need of involving a broad range of stakeholders in developing national strategies.

A national strategy is required to develop new approaches that provide incentives and funding mechanisms to support bioinformatics joint research across academic disciplines and economic sectors. Investment in building native resources, instead of relying on ready-to-use external technologies, can secure a more sustainable development in biotechnology.

In addition, supporting the private sector and small software industry is essential to create productive synergy between academia and industry.

Human Resource Development

Human resources are the key factor in bioinformatics, but developing these resources requires a painstaking investment that has proved to be a challenging task even in the developed countries. Most developed countries started their training in the form of short training courses that were done by small groups of enthusiastic scientists (Ranganathan, 2005). Subsequently, several universities realized the importance of creating postgraduate programs through the involvement of academic and research staff from disparate disciplines. Students joining these programs come from diverse backgrounds and usually faced the problem of mastering topics and skills that are not related to their undergraduate training. The insufficiency of postgraduate practical skills and the large demand of the private sector prompted several universities in the developed countries to design undergraduate curricula dedicated to bioinformatics or genomics coupled with bioinformatics. The scenario in several newly industrialized countries was very similar with the difference in time of onset, which came several years later (Palacios and Collado-Vides, 2007; Zeti et al., 2009; Kulkarni-Kale et al., 2010).

The interest in bioinformatics training in the Middle East region started a decade ago. Most activities took the form of short training courses dedicated to a specific topic such as biological databases, sequence analysis, and phylogenetics. At the beginning, nearly all of the training initiatives were sponsored by international organizations such as ICGEB and UNESCO and were usually carried out abroad (Pongor and Landsman, 1999). Some online courses such as the one provided by Star alliance group, constituted an attractive opportunity to those who have financial constrains to travel. In the last few years several training initiatives were launched locally in countries like Turkey, Iran, Egypt, Jordan, Lebanon, Palestine, and Syria. Organizing short training courses or workshops usually faces a funding problem. Therefore most of these courses were isolated events that could not generate significant momentum. Nevertheless, the short training courses can be a good tool to introduce bioinformatics both to inquisitive biologists and computer scientists in order to increase their awareness about this field.

Currently a few postgraduate programs exist in the region that either focus solely on bioinformatics or teach it in the context of related programs such as biotechnology or computer sciences. Turkey and Iran were the first to consider establishing such programs at the M.Sc. and even at PhD. levels. In these two countries the need for well trained bioinformaticians is steadily increasing to meet the needs of research institutes and a handful of bioinformatics companies that are expecting growing demand from the international market. Another example of a graduate program in bioinformatics is the one at Palestine Polytechnic University in which the bioinformatics track of the informatics master program got the benefit of several existing computer, IT and biotechnology programs that are integrated in society-relevant services.

Despite the abundance of staff in biology, computer science and information technology in most universities, there is no single undergraduate program in bioinformatics in the region. Moreover, most of the undergraduate curricula related to biosciences do not have bioinformatics courses. Only few biotechnology undergraduate programs have one bioinformatics course, which is usually not considered as a major obligatory course. Therefore, an attainable action to promote development of bioinformatics education would be to introduce and increase the weight of bioinformatics courses at the undergraduate level for both bioscience and computer science related disciplines.

Since bioinformatics is typically less capital-intensive resources compared with other technologies, countries of the Middle East have to seriously consider investment in human capacity building in this field. We have to recall that a 10 year investment in bioinformatics human resources has generated a significant national income in a country like India (Takeuchi and Nomura, 2008). Unlike developed countries, where the declining birthrate is a main problem, more than 50% of the Middle East population is of the age less than 25 years and with immense informatics talent. The investment in this young generation can play a key role in creating a more prosperous future

Infrastructure and Facilities

A typical genomics and bioinformatics project would pass through three stages, namely, the high-throughput data generation stage, the data storage and management stage, and the data analysis stage (Figure 3). Genomics requires costly infrastructural investment to build high-throughput laboratory facilities and instrumentation that are necessary for data generation. Once the data is available the next step, which consists of data storage and management requires a high-capacity, yet moderately expensive hardware. The most exciting part is the data analysis which does not actually require expensive investment. It rather needs a set of affordable communication networks, software, and processing units.

Currently there is no center in the region dedicated for high-throughput genomic research that can lead to the generation of biological data from indigenous resources. However, Turkey is seriously considering the establishment of a genomic and bioinformatics center that will be dedicated

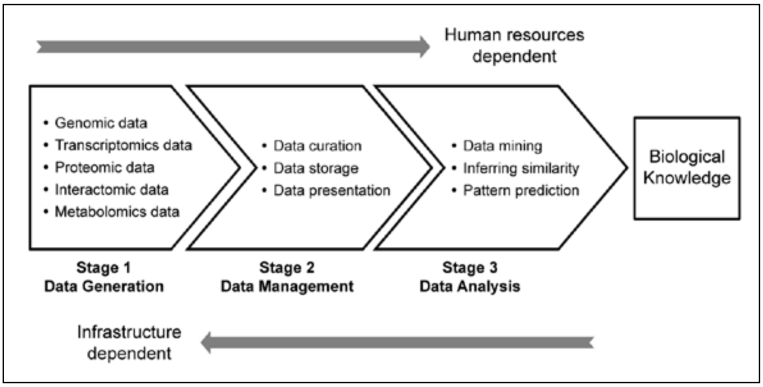

Figure 3. Flow Diagram of Biological Data. The diagram shows the three main stages of a typical genomics and bioinformatics project.

to large scale genomic projects, both for the benefit of national and regional biomedical and biotechnology programs (personal communication; Dr Bayram Yuksel).

Countries like Saudi Arabia and Iran have some interesting efforts that are worth mentioning. In 2008, Saudi Biosciences, which is a biotechnology company, launched a project to perform sequencing and analysis of the so called Arab human genome using DNA from 100 different individuals from the Arab population. The project was an international joint collaboration with Beijing Genomics Institute and CLC-bio, which is a bioinformatics company (www.medicalnewstoday.com/articles/120893.php).

In June 2010, the genome of the Arabian camel, Camelus dromedarius was completed through a joint project between Saudi Arabia's King Abdulaziz City for Science and Technology and Beijing Genomics Institute (BGI, 2010). On the other side of the Gulf, Iran has also started a project to map the genetic markers of what they call the Iranian human genome so as to understand Iranian genome diversity (Banihashemi, 2009).

Concerning data storage and management, a promising project started its pilot phase last year at Nile University, Egypt. The project includes the development of the Nile University Bioinformatics Server (NUBIOS), which is a unique national and regional project that hosts novel software tools and is expected to mirror some popular public databases (Abouelhoda and Ghanem, 2010) .

Despite the wide range of medical, agricultural and natural resources that deserve great attention, there are only a few publically available bioinformatics databases that describe original data from the region. One of these databases is the Arabian Camel Expressed Sequence Tags (EST) database host by King Abdulaziz City for Science and Technology (http://camel.kacst.edu.sa). This database contains 70,000 EST sequences from the camel cDNA libraries. It enables data analysis with some useful tools and with the possibility to add sequences from the public domain (Al-Swailem et al., 2010). There are two additional initiatives towards creating biomedical data sources. They are the "Catalogue for Transmission Genetics in Arabs" (CTGA) database (www.cags.org.ae) (Tadmouri et al., 2006) and the Iranian Human Mutation Database (www.ihmd.hbi.ir). The two databases aim at creating databases for genetic diseases described in the region that would facilitate sharing biomedical information and expertise.

Partnership and Networking

Bioinformatics is without any doubt an example of a multidisciplinary field that was formed by people from a broad set of backgrounds. The fact that bioinformatics development requires a combination of diverse specialists makes this field both exciting and challenging.

Most universities in the Middle East lack the culture of dialogue between traditional academic disciplines. For example departments such as biology, computer science and statistics may sometimes share the same faculty and even the same building, nevertheless, an exploration of their publications shows little joint collaboration among researchers in these departments. These rigid disciplinary boundaries should be broken down to pave the way for new educational and innovative research areas in natural sciences.

The idea of establishing a genomics and bioinformatics network in the Middle East region was recommended early during the Genomics and Public Health Policy Executive course that was held in Oman in 2003 and organized jointly by the World Health Organization's Eastern Mediterranean Regional Office (WHO/EMRO) and the University of Toronto Joint Centre for Bioethics. The aim of the course was to assess the potential of genomics to address health needs in the Eastern Mediterranean Region (Acharya et al., 2005). Following that recommendation, the Eastern Mediterranean Health Genomics and Biotechnology Network (EMHGBN) was established in 2004. However, there has been little engagement by the bioscience community with this network. It seems that with the presence of several international bioinformatics networks, there is less interest to establish and maintain such national or regional networks.

Having an effective regional bioinformatics network can be an excellent opportunity for the countries of the Middle East. It can serve as an environment to promote productive interaction across institutions to share data, expertise, training, legislation and regulation, and intellectual property guidelines. In addition, networking can also open many new exciting opportunities for the region; especially through encouraging teams from neighboring countries that share similar interests to create joint research projects.

To successfully develop bioinformatics and genomics research in the Middle East, it is imperative to create new international cooperation initiatives and to strengthen the existing ones. The fast evolution nature of these technologies requires close cooperation with renowned universities and research institutions to keep up with the latest developments. In addition, such cooperation is expected to open new opportunities for the gifted students to pursue their graduate degrees with good international research groups

Conclusions

Bioinformatics and genomics are instrumental tools in the development of natural sciences and technologies. Despite the fact that Middle Eastern countries are still lagging behind in these two disciplines, there are great opportunities lie before these countries to move forward in adapting and applying these disciplines to the benefit and prosper of their societies. There is a need to:

- Adopt new policies and strategies at the national level to ensure the adaptation and implementation of these cutting-edge disciplines in health, agriculture and environmental fields and their sustainability.
- Establish a culture of adapting society relevant applications to meet the local needs.
- Build concentrated research/teaching centers in bioinformatics and genomics to overcome the shortage in human and infrastructure resources.

- Instigate more productive networking with local and international institutions and industries.
- Support the existing bioinformatics initiatives so as to enable other researchers to build upon them.
- Establish a regional bioinformatics and genomics society to ensure collective work and data sharing.
- Increase the awareness of bioinformatics and genomics among university academics, software industry, and governments' agencies.

Acknowledgements

I wish to express my deep gratitude to Dr. Robin Abu Ghazaleh and Dr. Fawzi Alrazem for their valuable contribution to this paper.

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The Bioeconomy to 2030: Designing a Policy Agenda*

Michael Oborne

Biotechnology has steadily evolved to become a potential motor of environmentally sustainable production and a proven source of a diverse range of innovations in agriculture, industry and medicine. Could we be at the dawn of a new bioeconomy? Public policies will influence the answer.

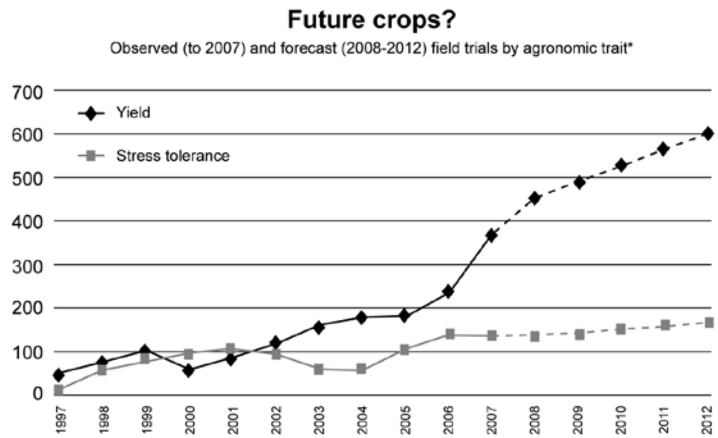
Since the dot.com boom years, debates have raged about where the future sources of rapid growth will lie. Biotechnology has been one widely cited candidate. But experts are divided: some laud biotechnology as a solution to problems such as overcoming disease and boosting food supply, while others see it as a risky and invasive technology.

Can the biological sciences overcome these differences, not only to contribute to solving complex global problems, but to become a driver of economic and societal progress? This is where a bioeconomy comes in. An easy way to think about this idea is to imagine a world driven by a marriage of biology and technology, rather than, say, communications or oil.

However, rather than narrow biotechnology down to some 'killer app' such as the micro-chip or the internal combustion engine, consider it more in terms of its pervasiveness and potential to drive whole areas of the economy in different ways.

Already a substantial share of economic output is partly dependent on the development and use of biological materials. This fact alone has attracted considerable government attention.

* First published in **OECD Observer** on March 2010. Oborne, M, "The Bioeconomy to 2030: Designing a policy agenda", OECD Observer No. 278 March 2010. www.oecdobserver.org



The OECD has been examining biotechnology for decades, and in 2006, our International Futures Programme launched an interdisciplinary, strategic project to examine the future of a bioeconomy and the way in which policy action could shape its longer term development.

What have we found out? One key message is that the contribution biotechnology could make to economic activity is significant. By 2030 the use of biotechnologies is estimated to contribute up to 35% of the output of chemicals and other industrial products that can be manufactured using biotechnology, up to 80% of pharmaceuticals and diagnostic production and some 50% of agricultural output.

Even without new policies or major breakthroughs, biotechnology could contribute up to approximately 2.7% of GDP in the OECD by 2030. For developing countries this share could be higher, thanks to the greater importance of primary and industrial production in overall output. Moreoever, as these figures assume business as usual, they probably underestimate the potential effects on energy, health and farming.

A striking implication of these estimates is that the economic contribution of biotechnology is potentially greatest in industrial applications, with 39% of the total output of biotechnology in this sector, followed by agriculture with 36% of the total and health applications at 25% of the total.

Also striking is how much these estimates are out of step with the present focus of R&D expenditures by businesses, where a massive 87% of private sector biotech R&D investment went to health applications in 2003, but only 4% on primary production and just 2% on industrial applications.

This mismatch could partly reflect higher R&D productivity in agricultural and industrial biotechnology compared to health biotechnology, though a lack of policy incentives, supporting regulations, skilled researchers and a public lead in R&D investment could also play a role. If a bioeconomy is to properly unfold, then this is a mismatch which policymakers can help correct.

Building in the short Term

A closer look at biotechnological developments will make these conclusions clearer. Consider the three main sectors where biotechnology can be applied: primary production, healthcare and industry. While primary production includes all living natural resources, including forests, plant crops, livestock, insects and marine resources, the main current uses of biotechnology are for plant and animal breeding. The main human health applications are therapeutics, diagnostics and pharmacogenetics to improve prescribing practices. Then there are industrial applications which include the use of biotechnological processes to produce chemicals, plastics and enzymes, environmental applications, such as bioremediation, biosensors, methods to reduce the environmental effects or costs of resource extraction and the production of biofuels.

How advanced are these? To be sure, several applications, such as biopharmaceuticals, diagnostics, some types of genetically modified crops and enzymes are comparatively 'mature' technologies. But many other applications in areas such as biofuels and bioplastics have limited commercial viability and rely on supportive policies or are still in the experimental stage, such as regenerative medicine and health therapies via cell-based RNA interference. Based on these advances, it is possible to predict some near term impacts of biotechnology with some precision, thanks in part to regulatory requirements for some agricultural and health biotechnologies that leave a data trail about what will possibly reach the market over the next five to seven years.

Also, while biotechnology is frequently used as a process technology to make existing products such as fuels, plastics and crop varieties, it can also be used to produce entirely new products, such as anti-cancer medicines. In these cases, the problems that need to be solved are already quite well known, from the diseases to the types of crop traits and biomass with the potential to improve agricultural and industrial outputs.

The size of the potential market for products such as biofuels or anti-cancer drugs can also be estimated with reasonable accuracy, though there are many unknowns, about the rate of technological advance in other, nonbiotech cancer treatments and so on.

Take agriculture, where the use of biotechnology is developing fast. By 2015, approximately half of global production of the major food, feed and industrial feedstock crops could come from plant varieties developed using one or more types of biotechnology.

These biotechnologies include not only inter-species genetic modification but also intragenics, which involves the transfer of genes between species that are able to crossbreed, gene shuffling, which targets traits to improve cell performance, and marker-assisted selection, which helps identify and select those traits of possible value for productivity, disease resistance, quality and the like.

Research into how biotechnology can improve both yields and resistance to stresses such as drought, salinity and high temperatures has increased rapidly since the late 1990s, as shown by the increase in the number of GM field trials (see chart). Research results are useful for finding out which crop varieties with agronomic traits could be ready for the market between 2010 and 2015, particularly for major food and feed crops such as maize and soybeans. Some of the agronomic traits will also be available for alfalfa, cotton, potato, rice, tomato and wheat varieties. Biotechnologies, other than genetic modification, are likely to be widely used to improve the quality and health of livestock for dairy and meat.

Healthcare is also reasonably straightforward to predict in the short term, with biotechnological knowledge ready to play a role in most therapies by 2015, including both small molecule and large molecule biopharmaceuticals, and with the design of clinical trials and prescribing practices being influenced through the use of pharmacogenetics.

As for industry, the value of biochemicals (other than pharmaceuticals) could increase from 1.8% of all chemical production in 2005 to between 12% and 20% by 2015. Biofuel production, for instance, could partly shift from starch-based bioethanol to higher energy density fuels manufactured from sugar cane or developing bioethanol products based on lignocellulosic feedstock such as grasses and wood.

All of these scenarios suggest a thriving biotechnological sector, but more is needed for this to become a bioeconomy in the longer term, say, by 2030 and to reach the levels of contribution to GDP our figures suggest it can. A successful innovation system is needed for this to happen.

Biotechnology R&D must be performed, paid for and result in commercially viable products and products. This process is influenced by many factors, including regulatory conditions, intellectual property, skills and development. Social attitudes, market structure and business models will also play a role. Improvements can be made to policy in many of these areas.

Regulations are needed to ensure the safety and efficacy of biotechnology products. But regulatory costs are an influential factor. For instance, regulatory costs for genetically modified plant varieties (ranging in the US from $0.4 million to $13.5 million per variety) have limited the use of this technology to a small number of large market crops, while the costs for the open release of genetically modified micro-organisms (approximately $3 million per release in the US) have held back deployment of techniques, such as bioremediation to clean up polluted soils. In some cases these costs reflect social concerns about health and safety, and these concerns have to be allayed. However, in other cases, especially in agriculture, the costs may also reflect a disjointed global regulatory environment, with researchers and investors facing similar compliance requirements in different countries.

Creating a more internationally harmonised regulatory scene would help reduce these costs by creating a level and more transparent playing field that producers, not least those developing applications for small markets, and consumers would benefit from. Policy action to ease regulatory costs would give those technologies that are ready the market access they need to grow and improve. Intellectual property rights must also be harnessed for the bioeconomy to grow. There is an opportunity for both firms and universities to use IPR to encourage knowledge-sharing through collaborative mechanisms such as patent pools or research consortia.

This will influence new business models too. Two new business models could become increasingly important to 2030: collaborative models for sharing knowledge between entities and reducing research costs, which will bolster smaller biotech firms in agriculture and in industry, and integrator models that bring key protagonists together in areas such as healthcare to manage the complexities of predictive and preventive medicine, drug development and major database analysis

Designing a Policy Agenda

Clearly, realising a bioeconomy by 2030 will take work and require a policy framework for addressing technological, economic and institutional challenges across agriculture, health and industry. Mature biotechnology applications may need some minor assistance, but other areas of biotechnology, such as personalised medicines, need a major policy drive with new mechanisms. Such measures will have to manage crosscutting issues for intellectual property and integration across applications, and tackle local and global challenges, from investment and trade barriers to health and environmental concerns.

One of the promising prospects associated with bioeconomy is that its main markets will be in developing countries, reflecting rapid income and population growth. Rising levels of educational achievement across the developing world, particularly at the tertiary level, will create centres of biotechnology research that can address some of the problems that are likely to develop in these countries, including a growing need for low carbon energy, clean water and high-yield, resistant agricultural crops.

But whether the goal is to improve food security, enhance health therapies or boost the sustainability, safety and productivity of industry, obtaining the full benefits of biotechnologies will require leadership, primarily by governments but also by important firms, as well as informed civil society and consumer groups. Regional and international agreements will likely be needed too, as will mechanisms to ensure that policy can flexibly adapt to new opportunities.

In short, the structural conditions required for success must be put in place. If this is done, then a dynamic and beneficial bioeconomy would take hold and brighten the long-term future of the entire planet.

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NOVEL APPROACHES IN MEDICINE AND HEALTHCARE

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Reducing the North-South Cancer Gap

Pierre Bey

The number of new cancer cases has rapidly increased all around the world. It will continue to increase in the next decades. If mortality rates from cancer have begun to decrease in industrialized countries, they will dramatically rise in developing countries due to lack of specific organizations and means for prevention, early diagnosis and treatment facilities. It is urgent for each country to build a long-term cancer plan adapted to local specificities to fight against cancers and avoid an announced disaster.

This urgency is related to at least three reasons:

- Epidemiology: cancer is now becoming a health challenge for all countries around the world
- Personalization of strategies and of treatments will change future care of patients with cancer
- Costs of treatments will continue to rapidly increase, all the more if they are not effective due to late diagnosis

The Burden of Cancer in the Coming Decades

Cancer incidence has rapidly increased in the last decades with a slow decrease in mortality rates in all industrialized countries, as in France.

	FRANCE 1980	**FRANCE 2005**
New cancer cases	170 000	320 000 (+90%)
Deaths from cancer	125 000	146 000 (+16%)
Population	54	63 m (+17%)

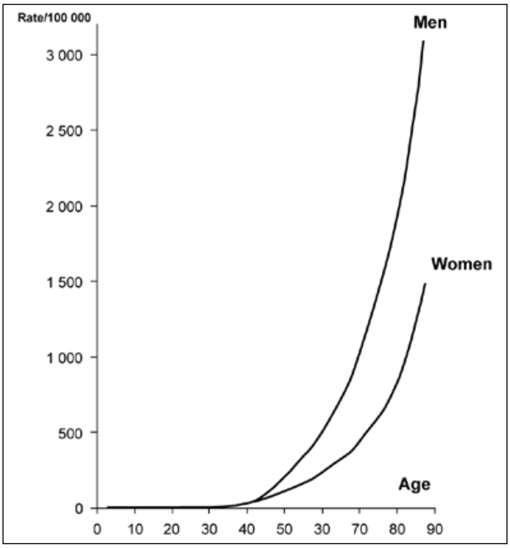

Figure 1. Cancer Incidence in France by Sex and Age

The main reason for this increase of cancer incidence is aging of the population: life expectancy in France was 45 years in 1900 and 81 years in 2005. Associated with this fact is that, even if cancer exists at all ages, cancer incidence increases quite exponentially with age in France as in all countries in the world (Figure 1).

Increasing life expectancy is related to the reduction of mortality in infancy, from infectious diseases and cardiovascular diseases which appear in all countries more or less rapidly, as in France (Figure 2).

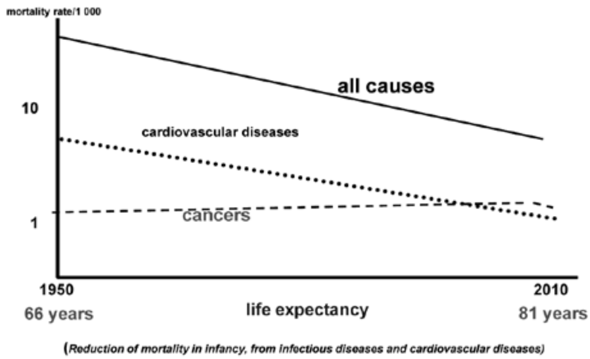

Figure 2. Evolution of Mortality Rate in France (1950–2010)

Cancer incidence will continue to increase in all countries, industrialized or developing. Two-thirds of new cancers are expected to appear in developing countries.

	NEW CANCER CASES 2000	NEW CANCER CASES 2020
Whole World	10 million	15 million (+50%)
Industrialized countries	4 million	6 million (+50%)
	(Pop. 1 billion)	(Pop. 1.1 billion) (+10%)
Developing countries	6 million	9 million (+50%)
	(Pop. 5 billion)	(Pop. 5.9 billion) (+20%)

The major difference will concern mortality. Today, cancer kill more people every year in south countries than AIDS + malaria + tuberculosis. The prevision done by the World Health Organization for developing countries are alarming.

	CANCER DEATHS 2000	CANCER DEATHS 2020
Whole World	6 million	9 million(+30%)
Industrialized countries	2 million	2.2 million(+10%)
Developing countries	4 million	6.8 million(+70%)

If success rates from cancer treatment do not change in the near future, a possible future scenario could be that shown in (Figure 3).

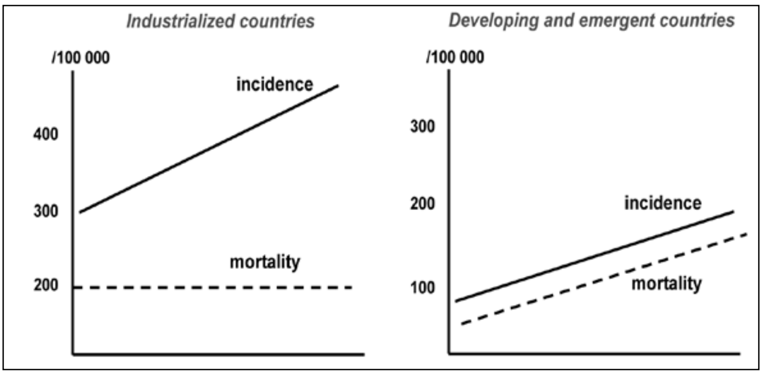

Figure 3. Evolution of Cancer Incidence and Mortality 1980–2020

The reason for this trend is that mortality from cancers depends on the following:

- Access to prevention, early diagnosis and to treatment facilities. These do not yet exist in most developing countries to the required standard. So, cancers are diagnosed at advanced stages in more than 80% of cases, when distant metastases are present and the tumor can no more be cured.
- One example is that of retinoblastoma, a rare tumor of the retina appearing in young children, and which is diagnosed at an early stage in western countries and cured in almost 100% of cases. In developing countries by contrast, it is diagnosed often at a very late stage and mortality rates can be more than 60%
- In breast cancer, early stage detection in a country such as France means that in 30% of cases, the potential for a cure is 90%. In a country such as Morocco, this is as low as 4%
- The most frequent cancers observed in developing countries are those with higher mortality rates such as lung cancer (>90% mortality), liver cancer (>90% mortality), stomach cancer (>70% mortality)

Personalized Medicine: A Revolution in Cancer Treatment

Today, most patients with cancer are treated using probability reasoning. Such treatments are often less effective, potentially toxic and always costly. By example for a breast cancer of 2 cm, with one lymph node involved, most patients will receive adjuvant therapy after surgery; six months of chemotherapy; six weeks of radiation therapy and five years of hormone therapy. The cure rate is 60% with surgery alone, 70% with the addition of radiotherapy and 80% with the addition of radiotherapy, chemotherapy and hormone therapy. So, radiotherapy, chemotherapy and hormone therapy are used for 80 to 100% of patients with a benefit for only 10 to 30%. [Are you saying that only 10 to 30% of cancer patients benefit? This is a little unclear. Please explain]

In the near future, with new imaging and biological tools (biomarkers), we should be able to characterize each tumor and each patient to define the best strategy and the best appropriate drugs (known as targeted therapy). For example, we know that hormonal treatment may be efficient only if hormone receptors are present on the tumor cells. More recently, we know that Trastuzumab, a monoclonal antibody, is effective in only 20% of breast cancers which overexpress a specific growth factor that we are able to detect on a tumor sample.

The consequences of such targeted interventions will be: higher efficiency, less toxicity, lower cost or at least a better utilization of expenses, but only if these tools are available.

Costs of Treatments Will Continue to Rise

Treatment costs are rapidly increasing with stage of the tumor at diagnosis, while survival is rapidly decreasing with stage of the tumor, which represent a kind of "double penalty" for developing countries. [Do you mean here: 'Treatment costs are more expensive if cancers are detected at a later stage – which represents a kind of double penalty for developing countries?].

In France, the mean cost of breast conserving surgery and breast irradiation at an early stage of cancer diagnosis is about 6.000 Euros. In Morocco, it is 2.500 Euros. At metastatic (later) stage of diagnosis, breast cancer treated by chemotherapy + hormone therapy + targeted therapy will cost about 40 000 Euros per year in both France and Morocco. The best way to decrease costs is to develop early diagnosis and personalized medicine, to limit unnecessary expenses.

Preventing a Future Crisis

We have to be collectively aware of the urgency and the need to undertake reflective and coordinated actions.

For effective fight against cancers:

- It is necessary to elaborate in each country (South and North) a national global long-term cancer plan, from prevention to rehabilitation after treatment, including research at each step, annual priority actions with realistic objectives according to local socio-cultural specificities and cancer types, and to find the necessary finance
- Such a plan has to be supported at the highest political level of each country and to be drawn up with professionals and for the patients and the population.
- Improved collaboration between South and South, and also between North and south through organizations such as the World Heath Organization (WHO), Atomic International Energy Agency (AIEA), Union Internationale Contre le Cancer (UICC), International Network for Cancer Treatment and Research (INCT). Also, through direct cooperation between institutions from North and South

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Increasing Access to Cancer Treatment

Ahmed Elzawawy

With increasing costs of novel cancer drugs and radiotherapy, and with increasing incidence of cancer, cancer treatment in the next decade in Low and Middle Income Countries (LMCs) is likely to become even less affordable for patients from low income backgrounds. A proposal by ICEDOC's Experts in Cancer without Borders [(ICEDOC) International Campaign for Establishment and Development of Oncology Centers, www.icedoc.org] is a potentially win-win situation by lowering costs of treatment by cancer drugs and radiation of breast cancer as a first model that would extend to other cancers.

Introduction

By the year 2020, there will be around 20 million new cancer cases, 70% of them in countries with only 5% of the total resources for cancer control (Stewart and Kleihues, 2003). Hence, it could be estimated that, at present, at least half of cancer patients in the world have no access to reasonable and systemic chemotherapy. The percentage is higher for radiotherapy and the picture is more tragic in Africa. With increasing costs for novel cancer drugs and radiotherapy and with the increase of incidence of cancer, we assume that in the next decade in Low and Middle Income Countries (LMCs), there would be more difficulties in affordability of treatment. Disease-free survival rates, cost effectiveness and cost utility are not increasing in a measure commensurate with the expenses of treatment. Moreover, we assume that the leading pharmaceuticals and radiotherapy equipment companies would face more difficulties in marketing their products in LMCs (Elzawawy, 2008 and Elzawawy, 2009).

Breast cancer is the most frequent malignancy among females. Multiple treatment modalities and drugs are used in its management (Stewart and Kleihues, 2003). Starting with breast cancer systemic therapy BCST as a first model, a new initiative of ICEDOC's Experts in Cancer without Borders [(ICEDOC) International Campaign for Establishment and Development of Oncology Centers, www.icedoc.org] proposes developing actionable and scientific strategies for resource sparing , cost effective and affordable cancer treatment that would be tailored to different regional conditions in the world (Elzawawy, 2008 and Elzawawy, 2009).

Lowering the Costs of Radiotherapy

We cite examples of the published and ongoing scientific ways of resource sparing by:

1. Shorten fractionation for post operative radiotherapy (Hypofractionation): The example of the UK standardization of breast radiotherapy (START) randomized trial B in which a radiation schedule delivering 40 Gy in 15 fractions offer rates of local-regional relapse and late adverse effects at least as favorable as the standard of 50 Gy in 25 fractions (START Trialists' Group, 2008)
2. Less number of radiation fields: Since systemic adjuvant therapy is given to most patients today, the traditional radiotherapy technique has been modified, it is no longer recommended that patients who have undergone complete or level I/II axillary dissections should receive full axillary radiotherapy since survival is not improved and the risk of lymhoedema is increased. Also, the isolated internal mammary chain failure is rare even when radiotherapy is not given (Truong et al. 2004).

For palliative radiotherapy of painful bone metastases: Shorten fractionation, up to a single fraction is preferred when examining the cost utility, despite the higher rate of retreatment associated with single-fraction radiotherapy (Van den Hout, 2003).

General measures: They could be done by the local professionals or in consultation with regional and/or international institutions and organizations particularly the International Atomic Energy Agency (IAEA) and its Program of Action for Cancer Therapy (PACT). These include:

a) general strategic planning of radiotherapy facilities in developing countries (Porter et al.1999) and the networking of three tier system of teleradiotherapy (Datta and Rajasekar, 2004); b) practical modification of the system of work to treat more numbers of patients, like to increase the hour work of cobalt machines and the increase the number of fractions a week from five to be six fractions in certain applications (Overgaard et al. 2006), and professional customized training for the local staff and maintenance (Porter et al. 1999). This because the local staff—and not the sophistication in machines—are the backbone of resource sparing and successful cost effective treatment for more number of patients.

By rough estimation of the above cited examples, and without additional high resources, it makes like that the facilities of radiotherapy in the world would be—at least—as doubled.

The PACT/IAEA has formed recently an Advisory Group for Increasing Access to Radiation Therapy in Developing Countries (AGaRT), that includes international experts from organizations, national representatives and in collaboration with manufacturers. ICEDOC is represented in this promising effort of PACT that—hopefully—could be turning point in the history of affordability of radiotherapy of cancer in many underserved regions in the world.

Breast Cancer Systemic Therapy (BCST)

In reviewing the current literature, we provide examples of innovative ideas, evidence-based approaches, and ongoing efforts that could decrease costs of BCST without compromising outcomes:

A) Relatively recent and expensive drugs

Evidence based cost effective indications of drugs: As the example of the limitation of the use of Trastuzumab in breast cancer to women with non-metastatic disease and known HER2/neu positive status (Yarney et al., 2008).

- The duration of treatment: As the example of the shorter course of trastuzumab in The Finher (Finland Herceptin Study) trial (Joensuu et al. 2004) and other European trials that use less total dose of the drug and shorter duration of treatment with preliminary results comparable to higher total doses. Hence, it could lead to less total cost of treatment that include less cost of the drug, less total time of hospitalization and less cost of the subsequent supportive treatment

- Changing the dose of drug and the duration of infusion: As the example of low dose, prolonged infusion of gemcitabine. This is based on application of the pharmacological information and how the drug gemcitabine is transformed to its active ingredient in the body (Zwitter et. al. 2005). Hence, the dose for one patient could be enough for four to five patients.
- The Glivec International Patient Assistance Program (GIPAP): It provides imatinib (Glivec) at no cost to patients with chronic myelogenous leukemia (CML) or gastrointestinal stromal tumor (GIST) and who have no access to Glivec in 81 countries (Lassarat and Jootar, 2006)
- Drugs interactions and pharmacokintetic based studies: As the example of lapatinib therapy. When Lapatinib was taken orally with food and beverage, containing CYP3A, such as grapefruit juice—and not on empty stomach as cited in its label us—it had an increase in its plasma level (Ratain and Cohen, 2007). Hence, for this expensive drug the dose for one patient could be enough for five patients
- Potential research questions include the interrupted courses of Aromatase inhibitors (AI) that probably would be also effective as continuous therapy after prior Tamoxifen and/or AI treatment. The hypothesis is that AI interrupted courses perhaps could enhance response of residual resistant cells (Colleoni and Maibach, 2007). This area is still in need for more researches.

B) Essential and conventional systemic cancer drugs

1. International measures and initiatives are needed for the assurance of bioequivalence of generics of off-patent drugs (Elzawawy, 2008).
2. Pharmcogenomic studies in order to guide the adjustment of the effective use of some drugs like Tamoxifen (Colleoni, 2002). Patients can be classified as poor, intermediate, or extensive metabolizers according to the genetic variation in CYP2D6, a key enzyme in Tamoxifen metabolism. In the poor metabloizers cases, the use of Tamoxifen, would be a waste of costs for five years of probably nonsense treatment and with unnecessary risks of hazards.

   On the other hand, a recent modeling analysis suggested that the benefit of five years of adjuvant Tamoxifen therapy in patients who were carriers of the wild-type CYP2D6 (the extensive metabolizers) was similar or perhaps superior when compared with the more expensive aromatase inhibitor therapy. Thus, a onetime test for CYP2D6 genotype has the potential to make the patient eligible for five years of savings by allowing for the use of—the less expensive—Tamoxifen, (Punglia et al., 2008) However, more prospective studies about CYP2D6 and this topic are needed

3. To test innovative combinations or different schedules of administration of older (and relatively cheaper) previously approved drugs that might lead to improve therapeutic index or more indications. Examples are:
    a. The use of relatively old drug like cisplatin in triple negative breast cancer patients (Gronwald et al. 2009).
    b. The metronomic use of prolonged, low oral doses of the cheap drugs cyclophosphamide and methotrexate as palliative breast cancer treatment (Colleoni, 2002).
    c. The more availability and the use of oral forms of chemotherapy that lower the cost of patient transportation, administration and hospitalizations and it may improve the quality of life (Elzawawy, 2008 and Elzawawy, 2009). In fact, this point could be applied to old and new cancer drugs. More researches are needed. Hence, most known cancers could have regimes of treatment that are totally or partially administrated via oral route. The pros and cons should be carefully studies in each community in a scientific and realistic ways.
    d. In a recent phase II trial, the low dose (6 mg/d) oral estradiol was effective (around 30%) as conventional high dose (30 mg/d) with less adverse events in postmenopausal women with advanced, aromatase inhibitor-resistant, hormone receptor-positive breast cancer (Ellis, 2009).

Finally we emphasize on these general measures

- To enhance researches and scientific studies that result in decreasing the total cost of treatment and to increase—or at least not to compromise—effectiveness and quality of life. It is preferred to design—as most as possible—protocols of treatment that require less or no hospitalizations—except in some cases, less costs of auxiliary cares and expensive supportive drugs that could be not available in the community or it would produce high additional financial burden.
- To develop more scientific researches that go with the notion of 'Resource-level-appropriate use of costly agents' and that necessarily involves inclusion of how to mobilize the locally-available resources and the establishment of viable partnerships with different sectors in the community
- To diffuse the concept of global and balanced cancer control in the communities. Earlier diagnosis of less advanced cases could decrease the total

costs of treatment and increase quality of life. But, screening and efforts for early detection without having affordable treatments that respect what we call 'The economic and social dignity of patients and their families' would be fruitless and it would be frustrating for both patients and health professionals (Elzawawy et al. 2008)

Conclusion

There are no indications that the costs of the novel cancer drugs and radiotherapy of cancer and the incidence and prevalence of cancer will stop increasing in the next decade. Hence, there would be more difficulties and challenges for patients, families, governments, physicians, industrialists, marketing and economists particularly in Low and Middle Income Countries (LMCs). There are ongoing different kind of approaches that are trying to lessen the problem by concentrating on direct donation of drugs only that could offer a considerable help, however, it would be far from the management of the problems of millions of cancer patients. Starting from December 2007, with communications, publications and meetings, the win-win initiative was proposed by ICEDOC's Experts in Cancer without Borders [(ICEDOC) International Campaign for Establishment and Development of Oncology Centers, www.icedoc.org]. The win-win initiative stress on the scientific approaches and in considering stakeholders in win-win scenarios in which no one would lose.

We explore the recent scientific approaches and potential prospects that could lead to lower costs of breast cancer drug and radiation treatment without significant evidence of compromising the overall outcome. The prices of drugs and equipment represent variable fractions from small to moderate parts of the total medical and social cost of cancer chemotherapy and radiotherapy; hence in the win-win initiative, we consider different factors globally. We started with breast cancer treatment as a model that could be extended to other cancers. The review of examples cited in this article for radiotherapy—if they applied widely—would result in doubling the number of treated patients with the present number of equipment. With the progress of efforts of PACT/IAEA with its new Advisory Group for increasing access in Radiotherapy in Developing Countries (AGaRT), then, a new turning point for affordability of radiotherapy could be achieved, if the movement continues. Regarding cancer drugs therapy, the total costs could be lowered without compromising the outcome. We recommend to adopt win-win scenarios and to create a think tank to foster innovative relevant scientific researches, thoughts and strategies that would aim at achieving cost-effective and accessible cancer treatment for more millions of patients with cancers in the world. ICEDOC is an organization, but the win-win initiative is not an organization itself. The win-win initiative is inspired from the works and publications of many. We don't claim patency. Hence, it is a concept and an approach that we call all for cooperation to be diffused widely, to be adopted and to be owned by all in the upcoming years. We emphasize on the importance of considering the broad sense for the term science and not to be taken as just the outcome of imported clinical trials. Hence, scientific cooperation, exchange of experiences, customized trials and respecting the realistic biological, human, social and economic conditions, cost—effectiveness, cost—utility and considering actual quality of life as end point adapted to each community are recommended.

Acknowledgements

I thank Prof. David Kerr, President of ESMO (European Society of Medical Oncology), Prof. Edurdo Cazap, President of the UICC (International Union against Cancer, Prof. Heinz Zwierzina, Austria and co-founder of ICEDOC, Prof. Gabriel Hortobagyi, former President of ASCO (American Society of Clinical Oncology and Prof. Martine Piccart, President Elect of ESMO, for their thoughtful discussion about the win-win initiative. My deepest appreciation to Dr. Pamela J. Haylock, PhD, RN, Secretary General of ICEDOC, Texas, USA and Mr. Dan Rutz, (ICEDOC), Sr. Communications Specialist, National Center for Health Marketing (NCHM), Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA for their precious advice and for the revision of the text of the first versions of the win-win initiative.

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The Hygiene Hypothesis and the Rise of Chronic Inflammatory Disorders

Graham A. W. Rook

Summary

As populations change from a traditional rural existence to the lifestyle of modern cities, there is a change in patterns of disease. Many infectious diseases decline, but chronic inflammatory disorders (allergies, autoimmunity, inflammatory bowel disease) increase dramatically, as do some cancers and mood disturbances. One reason for these frightening increases in serious disorders is defective regulation of the immune system due to depletion of microorganisms and parasites that accompanied man throughout evolution, and had co-evolved essential roles in setting up the mechanisms that regulate and terminate immune responses. In the absence of these organisms inappropriate inflammation can persist. The situation is aggravated by other environmental factors such as obesity, vitamin D deficiency and pollutants such as dioxins. This brief overview outlines the changes in patterns of disease, why the changes happen, and what might be done to prevent developing countries from encountering the same problems as their economies grow.

Introduction

The notion that a diminishing burden of infection in developed countries might partly explain the rising incidence of allergic disorders was suggested in 1989 when Strachan noted that in young adults a history of hay fever was inversely related to the number of siblings in their family when they were 11 years old (Strachan, 1989). Further studies confirmed that having many siblings, especially older ones, correlated with diminished risk of hay fever. So the 'hygiene hypothesis' was born. Initially it was thought that the common infections of childhood might protect from allergic disorders. However, excellent studies have indicated that these infections do not protect from allergies (Dunder, Tapiainen et al. 2007). On the other hand epidemiological studies have progressively identified specific organisms that do appear to protect from allergies, and these turn out to be organisms (viruses, bacteria and helminthes), often harmless, that co-evolved with man. We discuss the evolutionary reasons, and mechanisms of this protective effect below.

There was also a tendency to assume that the underlying reason for the increase in allergies in environments with diminished infections was overproduction of the Th2 lymphocytes that mediate allergic disorders. The reasoning was that most infections drive Th1 lymphocytes, which can oppose production of Th2 lymphocytes, so when infections are absent, more Th2 cells might be generated. According to this interpretation, the critical issue was Th1/Th2 balance, but this was a weak hypothesis. First, mediators such as IFN–g released by Th1 lymphocytes are present in large quantities both in asthma and in atopic dermatitis. Secondly, profound defects in the IL–12 or IFN–g (Th1) pathways do not lead to an increased incidence or severity of allergic disorders, implying that in man Th1 cells are not major regulators of Th2 responses. Thirdly, and most important, the Th1/Th2 balance hypothesis had been untenable since 1998 (Rook and Stanford, 1998), by time it was clear that there was a simultaneous increase in Th1–mediated chronic inflammatory diseases (Type 1 diabetes, multiple sclerosis, inflammatory bowel disease), (Bach, 2002) occurring in the same countries as the increases in Th2–mediated allergic disorders. Moreover, individuals infected by helminths, which enhance Th2 responses, are paradoxically less likely to have allergic disorders, and treating the helminth infection leads to increased allergic sensitization (Yazdanbakhsh, Kremsner et al. 2002).

Thus, the critical problem is not Th1/Th2 balance, but rather an increasing failure in the rich developed countries of immunoregulatory mechanisms that should terminate inappropriate inflammatory responses, whether Th1 or Th2, and whether targeting allergens, or self (autoimmunity) or gut contents (inflammatory bowel disease; IBD). As will be explained below, the implicated organisms are those that were present throughout human evolution, needed to be tolerated, and so co-evolved a role in priming immunoregulatory circuits; we have called these the 'Old Friends'. This situation is known as 'evolved dependence', and the mechanisms and organisms concerned are outlined later. These physiologically necessary organisms have become depleted from the modern concrete environment mainly because we are now separated from the animals, faeces, mud and untreated water with which we evolved.

The Balance of Effector to Regulatory T Cells

In support of this concept, immunoregulation has been shown to be faulty in individuals suffering from the diseases that are rising in parallel in rich developed countries: allergic disorders, and some autoimmune diseases, and probably in IBD too (referenced in full in Rook, 2009). It is clear that a failure of immunoregulatory mechanisms can indeed lead to simultaneous increases in diverse types of pathology, because genetic defects of Foxp3, a transcription factor that plays a crucial role in the development and function of regulatory lymphocytes, leads to a syndrome known as X-linked autoimmunity–allergic dysregulation syndrome (XLAAD) that includes aspects of allergy, autoimmunity and enteropathy.

Epidemiological Transitions

In order to be able to identify the relevant organisms, we need to understand the history of man's microbiology and changing exposures. In 1971 Omran coined the term 'Epidemiological Transition' to describe the major watersheds in human development that led to massive changes in mortality (discussed in Armelagos, Brown et al. 2005). Paleolithic populations carried the organisms that they inherited from their primate ancestors ('heirloom' species). These included multiple helminths, and those viruses that probably co-evolved with man (herpesviruses, papovaviruses (papilloma), adenoviruses, parvoviruses, picornaviruses such as enteroviruses and hepatitis A virus (HAV), perhaps hepatitis B), (Van Blerkom, 2003) and other important organisms (Helicobacter pylori, pinworm, Pneumocystis, Salmonella, Staphylococcus, and probably early forms of tuberculosis). In addition they would have been exposed to zoonoses that they picked up as they scavenged carrion (Armelagos, Brown et al. 2005). Finally, they will have consumed several milligrams of harmless environmental saprophytes every day, since these are ubiquitous in soil and water. We have called these 'pseudocommensals' because of their inevitable continuous presence until very recently. All of the organisms that have been found to be important for the hygiene hypothesis are found to be amongst those listed above, because of their extremely long, inevitable, constant association with man, often in harmless carrier states.

About 10,000 years ago, the shift to agriculture and husbandry created the First (Neolithic) Epidemiological Transition (Figure 1), (Armelagos, Brown et al. 2005). This will have had little effect on exposure to the 'pseudocommensals' or to the heirloom species. However the more sedentary lifestyle increased orofecal transmission, and caused prolonged contact with animals. The latter led to adaptation to man of a number of animal viruses (caliciviruses, rotaviruses, coronaviruses, orthomyxoviruses (influenza B & C), paramyxoviruses (measles, mumps, parainfluenza, smallpox), (Van Blerkom, 2003). In developing countries virtually all children are seropositive for rotavirus, which might therefore be relevant to the hygiene hypothesis. In sharp contrast, other viruses probably acquired during the Neolithic such as influenza (B & C), smallpox, mumps and measles cannot have become endemic until populations were large enough. This required communities of several hundreds of thousands, which did not occur until the appearance of cities 2–3 thousands years ago. Since this represents only 100–150 generations, extremely strong selection pressure would have been required for evolved dependence to appear, and this seems unlikely. Moreover most humans did not live in such large groups, and these viruses were, for example, absent from pre-columbian American populations.

In short, there were dramatic changes to man's microbial environment after the 1st Epidemiological Transition, but this did not result in loss of exposure to the organisms implicated by epidemiology in the hygiene hypothesis because until the modern era more than 97% of the population still lived in rural environments, close to mud, animals, and human faeces which were the sources of these organisms. The situation did not change until the mid 19th century.

Beginning in the mid 19th Century, some populations have undergone a 2nd Epidemiological Transition (Figure 1) in which public health measures and more recently, antibiotics, have resulted in diminished (or delayed) exposure to many of the organisms that were present in earlier eras. The changes to our microbiological environment caused by this 2nd transition are the ones that are contributing to the increases in chronic inflammatory disorders.

The Critical Organisms and their Immunological Role

These considerations allow prediction of the organisms involved in the 'Old Friends' hypothesis. From a Darwinian perspective we would expect the relevant organisms to have been present, inevitably and continuously, from relatively early in the evolution of the immune system ('Old Friends'). One would also anticipate a reliable mode of transmission such as the orofecal route, often accompanied by the ability to establish carrier states that facilitate such transmission. The orofecally transmitted organisms highlighted in recent studies of the hygiene hypothesis are particularly illuminating. These include *H. pylori, Salmonella*, Hepatitis A virus (HAV), enteroviruses and *Toxoplasma gondii* (referenced in full in Rook, 2010). Protozoa not yet considered in this context, to my knowledge, include the very ancient *Entamoeba*, *Giardia*, and *Trichomonas* all of which have lost their mitochondria and have a close association with humans.

The gut flora is also important. The profound immunological roles of gut microbiota and the presence of changes in the microbiota due to diet, hygiene and antibiotics are well established. The gut microbiota of people living in rich countries differ markedly in nature and diversity from the microbiota of people living in traditional communities, and these differences are enhanced by frequent exposure to antibiotics.

It is also likely that there have been dramatic changes to the composition of the skin flora (referenced in full in Rook, 2010). Before the invention of modern soaps and detergents, skin was probably colonized by ammonia-oxidizing bacteria. These are ubiquitous in soil, but they are exquisitely sensitive to alkylbenzene sulfonate detergents. Similarly, there have probably been changes in the flora of the lungs (which contrary to what is often assumed, are not sterile) and in the flora of breast milk.

Finally, some environmental saprophytes in mud and untreated water were so abundant in the hunter-gatherer, or early farming environment as to become 'pseudocommensals', consumed regularly and inevitably in milligram quantities. These too turn out to have immunoregulatory roles (Zuany-Amorim, Sawicka et al. 2002).

All of these organisms needed to be tolerated because they were harmless but always present in large numbers in food and water. The helminthic parasites needed to be tolerated because, although not always harmless, once they were established in the host, any effort by the immune system to eliminate them was likely to cause tissue damage. For instance, a futile effort to destroy *Brugia malayi* microfilariae results in lymphatic blockage and elephantiasis.

A cartoon of a major pathway by which these organisms are currently thought to prime immunoregulation and mediate protection from allergies, autoimmunity and IBD is shown in Figure 2, though no doubt other mechanisms exist. The host-parasite relationship evolved so that rather than provoking needless damaging aggressive immune responses, these organisms cause a pattern of maturation of dendritic cells (DC) such that these drive Treg rather than T helper cell 1 (Th1) or Th2 effector cells (referenced in Rook, 2009). This in turn leads to two mechanisms that help to control inappropriate inflammation. First, the constitutive presence of the 'Old Friends' causes continuous background activation of the DCreg and of Treg specific for the Old Friends themselves, resulting in constant background bystander suppression of inflammatory responses. Second, these DCreg inevitably sample self, gut contents and allergens, and so induce Treg specific for the illicit target antigens of the three groups of chronic inflammatory disorder. Release of the anti-inflammatory cytokines, IL–10 and TGF–b is often involved in the anti-inflammatory effects of these cells (Zuany-Amorim, Sawicka et al. 2002). These inhibitory mechanisms are aborted when there are legitimate 'danger' signals.

Immunoregulatory Effects of 'Old Friends' in Animal Models and in Clinical Trials.

The validity of this view is supported by clinical trials and experimental models in which exposure to microorganisms that were ubiquitous during mammalian evolutionary history, but are currently 'missing' from the environment in rich countries (or from animal units with Specific Pathogen-Free facilities) will treat allergy (Zuany-Amorim, Sawicka et al. 2002), autoimmunity (Zaccone, Fehervari et al. 2003) or intestinal inflammation (Summers, Elliott et al. 2005a). A striking example in human autoimmunity is a recent experiment of nature. Patients in Argentina suffering from multiple sclerosis were followed up for 4.6 years. It was found that those who developed parasite infections (which were not treated) had significantly fewer exacerbations than those who did not (Correale and Farez, 2007). Moreover, they also developed regulatory lymphocytes that specifically responded to myelin basic protein. In other words, the presence of the parasite appeared to drive the development of regulatory cells that recognised the autoantigen and inhibited the autoimmune disease process. Trials using helminthes have been performed in inflammatory bowel disease, using ova of the pig whipworm, Trichuris suis in ulcerative colitis (Summers, Elliott et al. 2005b) and in Crohn's disease (Summers, Elliott et al. 2005a). Formal trials with Trichuris suis are now planned in other chronic inflammatory disorders such as allergies and multiple sclerosis. Moreover, small companies marketing the ova have appeared, and many individuals are now testing the material informally on a patient by patient basis.

Pritchard and his colleagues in the UK have determined the maximum load of hookworm (*Necator americanus*) that can be tolerated without adverse effects. A Phase 1 trial in allergic rhinoconjunctivitis has been completed (Blount, Hooi et al. 2009), and further studies are in progress in allergies, multiple sclerosis and IBD.

There is also considerable potential for modulating inflammatory disorders by changing the intestinal microbiota. The most convincing data come from studies of gastrointestinal disorders, while studies in autoimmune and allergic disorders are less convincing. Nevertheless the power of the influence of the microbiota over the immune system is such that this is clearly set to develop into one of the major therapeutic tools in the future. We need to define and select appropriate probiotic strains, and to combine their use with appropriate antibiotics and prebiotics that favour growth or colonisation by selected organisms.

Other Chronic Inflammatory Diseases that might be Increasing as a Consequence of Altered Microbial Exposures

In addition to the allergic disorders, autoimmunity and inflammatory bowel disease, which have been considered in relation to the 'Old Friends' hypothesis in the past (Bach, 2002), there are several other disorders that are also increasing, and that are likely to be exacerbated or made more common by a switch in the balance of inflammatory to anti-inflammatory mechanisms.

Atherosclerosis

Atherosclerotic plaques are inflammatory lesions driven mostly by Th1 cells (Mallat, Ait-Oufella et al. 2007). IL–10 and TGF–b have a downregulatory effect on the development of atherosclerotic plaques (Mallat, Ait-Oufella et al. 2007), and in several experimental models transfer of regulatory T lymphocytes (Treg) will also inhibit atherosclerosis. Infection with *Schistosoma mansoni* inhibits atherogenesis in mice. There is similar evidence that IL–10 has a beneficial role in human atherosclerotic plaques (Mallat, Ait-Oufella et al. 2007).

Depression and Anxiety

Some stress-related psychiatric conditions, particularly depression and anxiety, are associated with markers of ongoing inflammation, even in the absence of any clinically apparent accompanying inflammatory disorder (Raison, Capuron et al. 2006). Moreover proinflammatory cytokines can induce depression, which is commonly seen in patients with cancer or hepatitis when they are treated with interleukin-2 or interferon-a, and can be treated with conventional anti-depressant drugs. Therefore some psychiatric disorders in developed countries, particularly the increasing levels of depression, might be attributable to failure of immunoregulatory circuits to terminate ongoing inflammatory responses, leading to prolonged 'sickness behaviour' and mood changes (Rook and Lowry, 2008).

Cancer

Many cancers are increasing in incidence in parallel with allergies, autoimmunity etc.; prostate cancer is one clear example. It is usually assumed that cancer is associated with excessive immunoregulation rather than too little, because many experimental systems have shown detrimental effects of Treg in established tumours. However, inflammation has a clear role in oncogenesis, causing DNA damage, and providing factors that promote growth, angiogenesis and metastasis (Porta, Larghi *et al.*, 2009). Thus inflammation contributes to the *initiation* of some cancers, and to the accelerated growth of others, so it is not surprising that in some experimental models regulatory T cells are protective (Erdman, Rao et al., 2010). In cancers like these, manipulations of the immune system to increase certain types of immunoregulation might be beneficial, and links between the hygiene or 'Old Friends' hypothesis and specific types of cancer should be sought.

The Future: How Do We Stop the Same Disease Trends from Occurring in Developing Countries?

This review attempts to show how a broad view of the hygiene or 'Old Friends' hypothesis, focussing on major changes in lifestyle that accompany the shift from hunter-gatherer to industrialised society, passing via herding and farming, can lead to an hypothesis that falls within Darwinian Medicine and has considerable explanatory power and practical application. It is of course clear that many other environmental changes also contribute to changing patterns of disease, and this brief overview does not intend to imply that diminished input of organisms that that have co-evolved an essential role as inducers of regulation of the immune system is the only factor. Obesity also becomes more common in developed countries, and obesity causes large increases in levels of inflammatory cytokines. So do vitamin D3 deficiency, and pollutants containing dioxins. But as each of these influences is identified, so we can start to stop or reverse the disease-inducing environmental changes. We listed a number of clinical trials that are taking place, using 'Old Friends' or probiotics as anti-inflammatory immunomodulators in a variety of inflammatory diseases, and many more are in preparation. Meanwhile, engineers and architects are thinking about ways in which beneficial organisms might be returned to the modern environment via air-conditioning systems, or by addition to water supplies, foods, or the final rinse in machines used to wash clothes and dishes. Hygiene should be aimed at protecting us from harmful pathogens, and should not

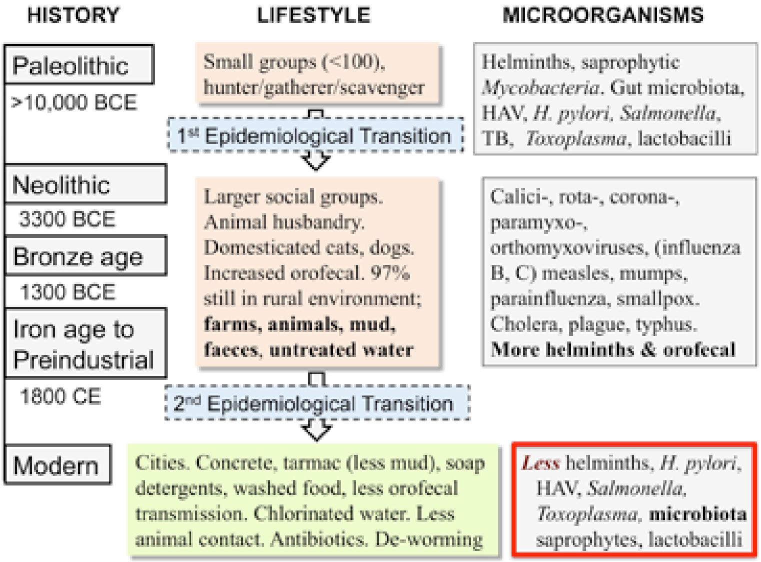

Figure 1. Human physiology was shaped by the hunter-gatherer way of life, which is regarded as the human 'Environment of Evolutionary Adaptedness'. Harmless organisms that were abundant in food and water (such as environmental actinomycetes) and helminths that had to be tolerated, developed a role in the induction of immuno-regulatory circuits. Without these there may be a failure to terminate inappropriate inflammatory responses, leading to an increased susceptibility to chronic inflammatory disorders, the precise nature of which depends on the genetics and history of the individual. This figure shows those some aspects of man's microbiological history that might be most relevant to the hygiene hypothesis. Epidemiological data, laboratory and animal models, and preliminary clinical trials investigating the hygiene hypothesis implicate several of the organisms (top right of the figure) that are thought to have accompanied mammalian and human evolution from at least as far back as the paleolithic. This relationship was clearly long enough for the establishment of evolved dependence. Organisms that evolved following the introduction of farming and husbandry during the Neolithic are less likely to be relevant in this context, and this 1st Epidemiological transition did not reduce human contact with organisms associated with animals, faeces and mud that had been present during the paleolithic. On the other hand the 2nd epidemiological transition might have led to gene-environment misfit, as the 'Old Friends' from the Paleolithic were progressively removed from the modern environment. The implicated organisms that are now depleted are shown in the red box at bottom right. (HAV= hepatitis A virus. TB= tuberculosis. CE=Current Era, BCE=before the Current Era).

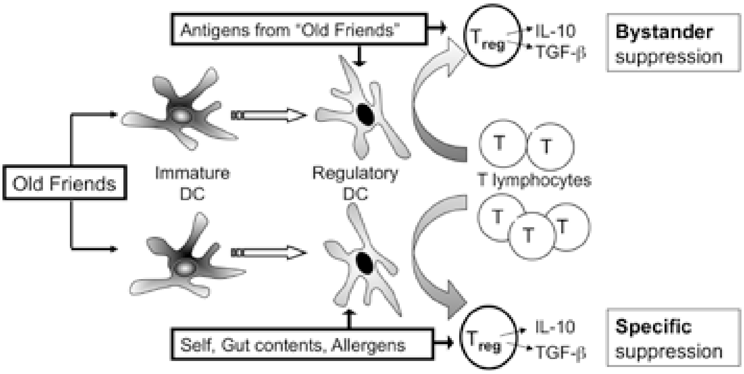

Figure 2. Organisms such as helminths and environmental saprophytes, that are part of mammalian evolutionary history ('Old Friends') and must be tolerated, are detected by the innate immune system and by immature dendritic cells (DC). These DC mature into regulatory DC that drive regulatory T lymphocyte (Treg) responses to the antigens of these organisms. The continuing presence of these antigens in the gut flora, in food, or resident as parasites such as microfilariae, leads to continuous background release of regulatory cytokines from these Treg, exerting bystander suppression of other responses, as shown in the upper arm of the figure. Meanwhile the increased numbers of regulatory DC leads to increased processing by such DC of self antigens, gut content antigens and allergens, as shown in the lower arm of the figure. Therefore the numbers of Treg specifically triggered by these antigens is also increased, downregulating autoimmunity, IBD and allergies respectively. This may be one the major mechanisms implicating the 'Old Friends' in immunoregulatory pathways, though there must be many others.

attempt to create microbiologically sterile environments. Humans are a part of the biosphere, and many of those organisms are essential parts of our physiology. If these insights are not exploited the currently developing countries will soon suffer from the same devastating epidemics of chronic inflammatory disorders that have become such a burden to the healthcare systems in the developed world.

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The Hygiene Hypothesis and its Impact in Public Health

Paolo Maria Matricardi

Summary

In populations progressively acquiring a 'westernized' lifestyle, the incidence of infectious diseases declines while that of allergic and autoimmune diseases increases. Many epidemiological studies suggest that the first phenomenon is contributing to the second one 'hygiene hypothesis'. A major role in the 'natural' prevention of allergic diseases is probably played by foodborne and faecal-oral infections. On the basis of current epidemiological knowledge, it can be predicted that 'mega-countries' undergoing epidemiological transition will have to face a sort of 'epidemic' of allergic and autoimmune diseases in the years to come. Public Health Systems of these countries may need to be prepared in advance for this event in order to avoid the mistakes of countries whose epidemiological transition occurred during the 20th century.

Introduction

Allergic diseases are more frequent in the general population than other immune-mediated disorders, such as autoimmune diseases or immunodeficiencies. Therefore, epidemiological studies investigating the hygiene hypothesis in relation to allergic diseases are easier to comply and have been performed much more frequently than those investigating the hygiene hypothesis in relation to Crohn's disease, multiple sclerosis, Rheumatoid Arthritis or other diseases related to dysregulation of the immune system. More than 1,000 research papers have been written on this subject and it is not possible to condense them in a few pages. In this chapter, we shall therefore try to summarize the most important pathways followed by research on the hygiene hypothesis as applied to allergic disorders: i.e. the allergy protective role of foodborne and orofaecal infections, starting from Strachan's initial observations and concluding with the most recent intervention studies.

The Birth Order Effect, i.e. the Hygiene Hypothesis for Allergic Diseases

In his seminal paper, David Strachan reported that in a British population the risk of having hay fever was directly related to socio-economic status (defined by the father's occupation) and inversely related to the overall number of siblings 'sibship size effect'; he also noted that hay fever was less frequent in the presence of older rather than younger siblings 'birth order effect'. Assuming that infections were acquired more frequently in large, less affluent families and earlier in the presence of many older siblings, Strachan proposed that exposure to common infections, especially very early in infancy or even through the mother *in-vitro*, may 'protect' from hay fever. As a corollary, he hypothesized that the decline in cross infections within young families due to decreasing in family size and to improvement in hygienic standards is, among the set of characteristics of the WLS, the one mostly responsible for the increase of atopy prevalence 'Hygiene Hypothesis'.

The direct association between socio-economic status (SES) and atopy has been repeatedly observed in developed countries, including USA, Italy and German adults. Similarly, the 'sibship-size effect' originally reported by Strachan have been reproduced in more than 20 cross-sectional studies. Finally, this phenomenon was confirmed also by a birth-cohort study involving 1035 US children. In this study, among subjects exposed early in life to other children at home or at day care, the risk of wheezing steadily declined with age, being high (OR 1.4) at the age of two-low (OR 0.8) at six years and very low (OR 0.3) at 13 years. These results suggested that bacterial or viral infections (facilitated by early contacts with other children) caused wheezing of infectious aetiology early in life, but in contrast inhibited atopic sensitisation and the subsequent development of allergic wheezing of atopic aetiology (asthma) later in life.

HAV Serology, Birth Order and Atopy: An Early Demonstration of the Hygiene Hypothesis

The hypothesis on the link between atopic sensitization and birth order was strongly supported by the results of a retrospective study among Italian young military recruits. In this study, young men with antibodies to hepatitis A virus showed a lower prevalence of atopy and atopic respiratory diseases; interestingly, this was independent of the number of older siblings and other relevant risk factors. Accordingly, the prevalence of atopy among seropositive subjects was always low, whatever the number of older siblings was, but among seronegative subjects was only low when they had three or more older siblings. This suggested that common infections acquired either early in life due to the presence of many older siblings (among seronegative subjects) or due to unhygienic living conditions (among seropositive subjects) may have reduced the risk to develop atopy. This study also suggested for the first time that faecal contamination of the environment—a condition which facilitates transmission of the hepatitis A virus—may protect from atopy. Following these observations, it was proposed that foodborne and orofaecal infections, through stimulation of gut-associated lymphoid tissues (GALT), Peyer's patches, and mesenteric lymph nodes, was protective against allergic diseases, autoimmune diseases and other immune-mediated disorders on the raise in the developed countries. This hypothesis did not completely exclude that airborne viruses may play a major role in regulating the development of atopy. Nevertheless, it suggested that the gut mucosa is a critical site among other sites where microbes may contribute to inhibit Th2-screwed immune responses against allergens that otherwise show deleterious effects in other mucosal areas (bronchial, nasal, conjunctiva). This hypothesis was in line with the concept that a proportion of the lymphocytes homing to the nasal, bronchial and enteric mucosa belongs to the same recirculating pool.

Evidence for an Allergy Protective Role of Foodborne and Orofaecal Infections

The hypothesis that foodborne and orofaecal microbes may protect from atopic sensitization was further tested by extending the observation on the same Italian military recruits. In a second study, it was found that atopy was inversely related not only to HAV positive serology but also to other orofaecal/foodborne infections (*Toxoplasma gondii, TG,* and *Helicobacter pylori, HP*), but not to infections mainly acquired through other routes. It was suggested that food hygiene and declining exposure to orofaecal microbes may underlay the allergy and asthma epidemic; moreover, the attention was focused on the gut mucosa and GALT as the sites where microbes may inhibit the development of the atopic phenotype. An inverse association of HAV, TG and HP with allergic diseases was replicated in a study conducted in a representative sample of the Danish general population.

Further support to this concept came from an analysis of the public data obtained in a large cross-sectional survey on a general population sample of the United States (Third National Health and Nutrition Examination Survey, 1988–1994). In this study, hay fever and asthma were less frequent in subjects seropositive for HAV, TG, and herpes simplex virus 1 versus seronegative subjects after adjusting for age, sex, race, urban residence, census region, family size, income, and education. Skin sensitization to peanut and to many airborne allergens was less frequent among HAV- seropositive versus HAV-seronegative subjects younger than 40 years of age. This study suggested that, in the United States, serologic evidence of acquisition of certain infections, mainly food-borne and orofaecal infection, is associated with a lower probability of having hay fever and asthma. An analysis of the data obtained after stratification of the subjects by year of birth produced a very interesting graph, showing that the epidemic trend of hay fever and asthma only was true in the subset of the US population who remained free of HAV infection up to the time of examination (Figure 1).

Studies in other settings supported the concept of an allergy-protective role of foodborne and orofaecal infections. In Norwegian recruits, the serological response to TG, but not to the respiratory encapsulated bacteria, was found to be associated with a lower risk for sensitization. Similarly, a positive HP infection status was inversely associated in Germany with

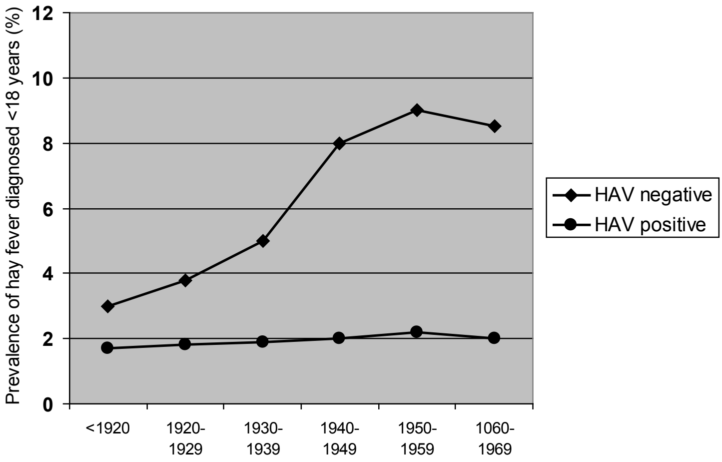

Figure 1. Prevalence of participants with a history of hay fever diagnosed before 18 years of age in relation to serology for HAV by decade of birth (NHANES III, 1988–1994). The prevalence of hay fever diagnosed at or before 18 years of age in HAV-seronegative subjects increased progressively from 2.7%, in cohorts born before 1920 to 8.5%, in cohorts born in the 1960s, whereas they remained constant at around 2% in all cohorts of HAV-seropositive subjects. (adapted from [11])

physician-diagnosed allergy and prescription of anti-allergic medication after adjustment for potential confounders (age, sex, nationality, smoking status and education of the participant). Among participants in the NHANES 1999–2000 aged 3–19 years, the presence of HP was inversely related to ever having had asthma.

Studies in Traditional Farms confirm an Allergy-Protective Role of Microbes

The hypothesis that foodborne and orofaecal microbes may protect from atopic sensitization was further supported by a long list of studies performed in farming environment. In these studies, direct exposure to stables where livestock is kept showed a strong protective effect against the development of atopy and atopic diseases. Evidence for a lower prevalence of atopic sensitisation among children raised in a farm came from studies in Finland, Canada, Austria and in many other countries.

Studies on the allergy protective role of the farming environment focused then on the components that mediate this phenomenon. The level of environmental endotoxin exposure was measured in homes of farmers' children, children with regular contact to livestock and control children with no contact to farm animals. Endotoxin concentrations were the highest in stables of farming families, but were also significantly higher indoors in dust from kitchen floors and children's mattresses as compared to control children from non-farming families. These data suggested that environmental exposure to endotoxin and/or other bacterial wall components was an important protective factor for the development of atopic diseases in childhood.

Further studies tried to disclose what (other) specific environmental factors mediate this protective effect of a farming environment. In a cross-sectional study in Shropshire (UK), farmers' children had significantly less current asthma symptoms and current seasonal allergic rhinitis but not current eczema symptoms or atopy. However, current unpasteurized milk consumption was associated with significantly less current eczema symptoms and a greater reduction in atopy. Moreover, unpasteurized milk consumption was associated with a consistent reduction in total IgE levels and higher production of whole blood stimulated IFN-gamma. The authors concluded that unpasteurized milk consumption was the exposure mediating the protective effect on skin prick test positivity. The effect was independent of farming status and present with consumption of infrequent amounts of unpasteurized milk. Other epidemiological studies confirmed that unpasteurized milk consumption is a protective factor against asthma, current wheeze, hay fever, current rhinitis, and atopic sensitization atopy eczema and allergic rhinitis, and asthma, rhinoconjunctivitis and sensitization to pollen, food and horse dander.

Which Foodborne and Orofaecal Microbes do the (Anti-Allergic) Job?

The hypotheses that HAV, TG, HP or other FB/OF infections play a causative role in the prevention of allergic sensitization and diseases is biologically plausible. However, the epidemiological studies generating this hypothesis did not offer any formal demonstration of such a role. A positive serology for these infections could, therefore, be interpreted just as a marker of exposure and acquisition of different categories of infections transmitted through contaminated food or the faecal-oral route. The next question in this component of the hygiene hypothesis was therefore: which kind of foodborne and faecal-oral infections do protect from allergic sensitization and allergic diseases? In principle, three categories of infections could be taken into consideration: (i) severe pathogens, (ii) commensals, and (iii) mild pathogens.

The first category includes microorganisms which can cause fatal diseases such as, the Vibrio colerae. From an evolutionistic point-of-view, however, it is very unlikely that a fatal infection contribute to shape the immune system to provide a protective influence against immune disorders. Although this hypothesis cannot be totally discarded, it is much more likely that either commensals or mild pathogens, or both play an important educating role on the immune system. This hypothesis will be discussed in the next two sections.

Do Commensal Bacteria of the GI Tract Protect From Allergic Diseases?

It is known since the seventies that mice reared under sterile conditions do not develop a fully functional immune system and that they are not susceptible to the induction of oral tolerance. The relevance of these observations for the understanding of atopy in humans was for a long time overlooked. A 'commensal' hypothesis emerged in the late nineties when *Lactobacilli* and *Eubacteria* were observed more frequently in the intestinal microflora of 1-year-old infants living in a country with a low prevalence of atopy (Estonia), while *Clostridia* were more frequent in age-matched infants living in a nearby country with a high prevalence of atopy (Sweden). It was therefore proposed that the gastrointestinal microflora of westernised children may predispose to atopy because of the stable predominance of bacteria stimulating TH2 activation (e.g. *Clostridia*) or because of the absence of bacteria that stimulate TH1 activation (e.g. *Lactobacilli*).

Data against the 'gut commensal' hypothesis came from a quite large birth cohort study performed in three European cities. The qualitative and quantitative composition of the faecal microflora of over 300 infants born in London, Rome a Goteborg was monitored seven times throughout the first year of age and related to the appearance of sensitization against food allergens and atopic eczema at 18 months of age. Neither atopic eczema nor food-specific IgE by 18 months of age were associated with time of acquisition of any particular bacterial group. The Authors concluded that their study did not support the hypothesis that sensitization to foods or atopic eczema in European infants in early life is associated with lack or presence of any particular cultivable intestinal commensal bacteria. However, a rather small nested case-control study of the same population, suggested that a reduced diversity in the early faecal microbiota of infants in the first week of life may be causally linked with atopic eczema appearing during the first 18 months of life.

Do Mild Pathogens of the GI Tract Protect from Allergic Diseases?

An interesting alternative hypothesis proposed that GI microorganisms, in order to protect from allergy, must stimulate the immune system with a pathogenic effect without causing a fatal disease. This category of microbes would include, by definition, mild pathogens. The analysis of the factors so far reported in the literature and summarized in the previous paragraphs may be of some help in identifying a good candidate to exert an allergy-protective effect within such category. Actually, atopy has been found to be less frequent among subjects who acquire faecal-oral and foodborne infections, in those exposed to stables and to high endotoxin concentrations, and consuming unpasteurized milk.Therefore, it was reasoned that an example of atopy-preventing infection may be found among gram-negative bacteria transmitted by contaminated food and the faecal-oral route, and by animals typical of farming environment. A number of infectious agents share these properties; among them, non-thyphoid *Salmonellae* were ideal candidates for an observational study since they cause diseases that are easily diagnosed even in early childhood. The hypothesis that acquisition of infection with *Salmonella* in the first 4 years of life may counteract the development of respiratory allergic diseases later in childhood was therefore tested with a longitudinal study design. In this study, the incidence of hay fever and asthma was compared in a group of Sardinian children (age 6–18 years) who had been hospitalized at preschool-age (at age <4 years) with salmonellosis (n=148) to that of age-matched children who had been hospitalized (at age <4 years) with acute enteritis of non-bacterial aetiology (n=168). This study showed that children who had been hospitalized with salmonellosis had a lower prevalence of allergic rhinoconjunctivitis or asthma than controls (Figure 2). The proportional hazard of salmonellosis for asthma was as low as 0.23 (95% CI: 0.08– 0.67; P<0.01) and for allergic rhinoconjunctivitis was 0.40 (95% CI: 0.17–0.95; P=0.04), after adjusting for a list of relevant confounders. The Authors speculated that acquisition of infection early in life by *Salmonella* may inhibit the development of atopic diseases and in particular of allergic asthma. They concluded that *Salmonella* may contribute to prevent the development of respiratory allergies through a range of mechanisms acting on the innate immune system, in a critical period for the maturation of immune response against ubiquitous allergens.

Other Mild Pathogens Protective against Allergies

Mycobacteria

In a trailblazing paper, (Shirakawa, et al.) showed in Japanese children immunised with BCG at 3 months of age an inverse relation between the magnitude of skin responses to intradermal tuberculin injection at 12 years of age and serum levels of total IgE, TH2 cytokines (IL–4, IL–10 and IL–13), and the prevalence of atopy and atopic diseases. These associations suggested that natural exposure to mycobacteria may be protective against atopy.

An impressive number of arguments support the concept that daily acquisition of mycobacteria through different routes may be essential to provide protection against allergic diseases and immune disorders. This aspect is in line with the hypothesis that the stimulation of the GI tract by mild pathogens is essential in protecting from allergies. Actually, an important route for the acquisition of environmental mycobacteria is

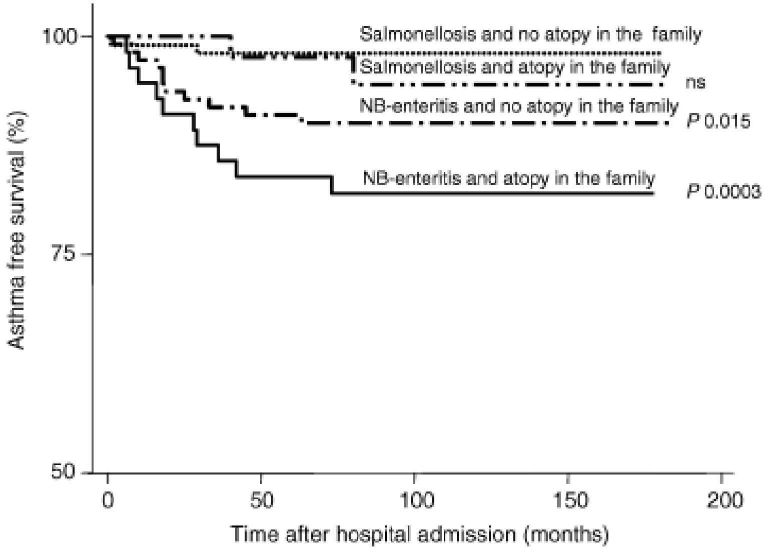

Figure 2. Asthma-free survival in children after hospitalization for enteritis, by aetiology of enteritis and family history of atopy (adapted from **[33]**)

their ingestion through contaminated food, contaminated water, and particles from contaminated soil. There is no doubt that in animal models mycobacteria can both prevent and treat allergic responses either by boosting TH1 or by driving allergen-specific regulatory T cells.

Helminths and the Hypothesis of Immunoregulation

Helminths were since the seventies proposed to protect from allergy and asthma either through the saturation of high affinity IgE–receptors on mast cells and basophils (by polyclonal IgE) or by induction of blocking IgG antibodies. Helminthic infections were associated with asthma in a few studies, but not in others. This area re-emerged when the immunosuppressive properties of helminths were re-evaluated by combining two new concepts: the 'anti-inflammatory network' (cytokines produced by regulatory T cells: interleukin-10, transforming growth factor-b) and the 'hygiene hypothesis'. Now helminths were considered to prevent allergy and asthma by stimulating the anti-inflammatory network, and the allergy epidemic was attributed to the sharp decline of helminthic infections. Indeed, chronic intestinal helminth infection have been shown to protect children from atopic reactivity in a variety of settings in developing countries. Similarly, worm infestation early in life (mainly Ascaris, Oxyuris) was negatively associated with subsequent eczema in a large population of East German children. In contrast, transient, delayed or milder forms of helminthic infections in children were positively associated with atopic disorders. To explain these new inconsistencies, it was speculated that early, heavy, and chronic helminthic infections protect children in endemic countries against allergies, e.g, by stimulating regulatory T cells and cytokines. Cross-sectional studies are clearly insufficient to answer whether helminths promote or suppress allergy and asthma. Theoretically, such a link could be experimentally investigated by monitoring either allergic children during a new helminthic infection or children chronically infected by helminths during de-worming treatment. Indeed, the latter approach saw that Venezuelan children chronically infected mostly with A lumbricoides and Trichuris trichuria developed or increased their atopic reactivity to mites after successful treatment with antihelmintic medication. Similarly, Gabonese children chronically infected by A lumbricoides and T trichuria transiently increased their reactivity to locally relevant airborne allergens during a 3-year follow-up after antihelminthic treatment. In contrast, an antihelminthic programme in Ecuadorian schoolchildren reduced helminthiases without promoting atopic sensitization, allergic symptoms and exercise-induced bronchospasm during a 1-year follow-up.

Intervention Studies related to the Hygiene Hypothesis

The hygiene hypothesis has inspired or indirectly supported a new category of intervention strategies based on the use of microbial products for allergy prevention and therapy. They include the use of probiotics, oral bacterial extracts, mycobacteria, LPS derivatives, immunostimulatory sequencies of oligodeoxynucleotides (ISS-ODN), and products derived from helminths. Some of these approaches (oral bacterial extracts, probiotics) have so far given negative or inconsistent results, others (ISS-ODN) seem more promising, but have not reached a level of evidence for efficacy high enough to be recommended by international guidelines.

The one approach that has been most frequently investigated and promoted by the Industry is the attempt to prevent or treat allergic diseases with probiotic bacteria, such as *Lactobacilli* or bifidobacteria. Notwithstanding the lack of a rationale, the hygiene hypothesis has also been abused as a rationale to 'invent' probiotic functional food for patients with allergic disease. Trials have been performed to evaluate the putative preventive or therapeutic effects of probiotics in allergies. Initial studies have been highly criticized for their insufficient design or other weaknesses in data handling or data interpretation. The evidence provided so far was still insufficient to generally advise the use of probiotics for primary prevention or therapy of allergies, and consequently this approach is considered an experimental one by a Task Force of EAACI, the GINA group, and individual opinion leaders. The more recent literature therefore reinforced the statement that probiotic at this stage is not considered a therapeutical option for treatment or prevention of allergy or atopy according to guidelines.

Conclusions

After 20 years of research, we should try to see the whole epidemiological evidence around the hygiene hypothesis in a historical perspective. This approach can help us to understand the whole evolution of the phenomenon of allergic diseases and can be helpful in the interpretation of the status of the allergic and infectious diseases in different countries in a dynamic model (Figure 3). We believe that in a western country, when income and education improve dramatically (as it has been the case in Western Europe in the wake of the Second World War), the borders of low socioeconomic status remain fluid and relative. Historically, the least affluent of one generation end up adopting the lifestyle of the middle classes of the previous one. The rising trend in respiratory allergies among the poorest could be therefore seen as the natural continuation of epiphenomena that affected the richest socio-economic strata of the United States population in the first half of the 20th century to reach the middle classes in the 1950s and '60s and eventually cascade down to affect the least-advantaged Americans in the inner cities from the 1970s onwards. In this context, it can be speculated that the primary cause of the epidemic of allergic asthma in American inner-cities is the consequence of the deprivation of factors linked to infections which confer protection from atopy and airways allergic inflammation. Emerging cases of allergic asthma among the least affluent African American and

Hispanic communities are likely more severe because atopic susceptibility encounters concurrent, chronic exposure to secondary risk factors typical at any time of poor urban environments (high exposure to cockroaches, smoking, damp and inadequate access to healthcare). Inner-city asthma may thus be the final stage of a class-driven urbanization and westernization that started two centuries ago in the United States and that is only now coming full circle (Figure 3).

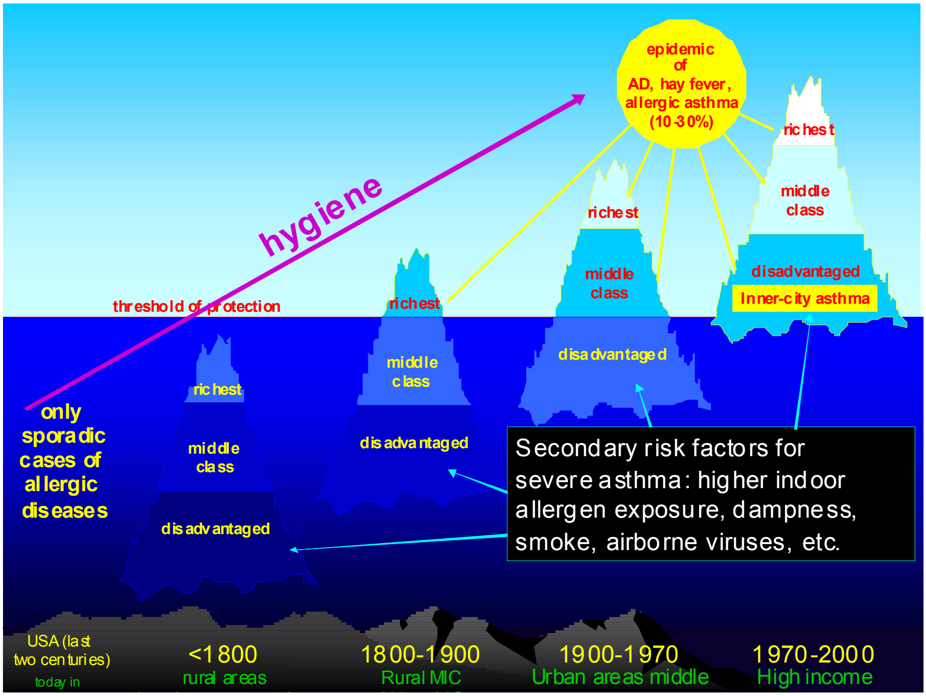

Figure 3. An historical perspective to the Hygiene Hypothesis (see text for explanations)

List of abbreviations

SES	Socio Economic Status
RAST	Radio Allergo Sorbent Test
CAP	CAPture
HAV	Hepatitis A Virus
ELISA	Enzyme Linked Immunosorbent Assay
TG	Toxoplasma Gondii
HP	Helicobacter Pylori
GI	Gastro Intestinal
Treg	T regulatory cells

Keywords

Allergic diseases, allergic immune response, atopy, asthma, allergic rhinitis, hay fever, atopic dermatitis, food allergy, prevention, hygiene hypothesis, farm effect, probiotic, and gut flora.

Aknowledgements

The Italian data reported here have been produced with the collaboration of many coworkers, and in particular the technicians of the Immunology Laboratory of the Italian Air Force Research Center in Pratica di Mare AFB (Antonio Palermo, Michele Fortini, Angelo Di Pietro, Roberto Vitalone, Antonio Rossi), the statisticians and epidemiologists in the Istituto Superiore di Sanitá in Rome (Luigina Ferrigno, Francesco Rosmini), the microbiologist and the statistician of the Ospedale Sandro Pertini in Rome (Carmen Bonanno, Valentina Panetta) and the Clinicians in the Paediatric Clinic of the University of Cagliari (Umberto Pelosi). Many scientists have contributed to develop the concepts here exposed. Among them, a special acknowledgement to Prof. David Strachan, SGHMS (London, UK), who elaborated the 'Hygiene Hypothesis' in 1989.

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Regenerative Therapy: Today's Dream, or Tomorrow's Discovery?

Mona K. Marei

Summary

For more than 50 years, tissue/organs transplants and bionic implants have been used successfully to replace human parts damaged by injuries or diseases. However, both of these methods have significant drawbacks. A new approach to tissue restoration is regenerative therapy, which promises to be one of the biomedical revolutions of the 21th century that can address the current unmet clinical needs. It derives its power from the application of the principles and methods of engineering and life sciences. Despite significant advances in the field, which have resulted in successful engineering of living skin, cartilage, bone…etc., the number of scientific challenges is increasing. The tissue function depends on cells (–10μm) to functional subunit (100μm – 1mm) that coordinate organ function with this complexity of native tissues, the engineering of living tissue is undergoing a major conceptual and methodological transformation in an effort to implement in vitro process that mimic in vivo tissue development. Indeed, recent work has indicated that interaction of concepts of developmental biology, engineering and manufacturing using could modify methods used currently to recapitulate phenomena as in vivo tissue development. The incorporation of improved fabrication strategy has led to dramatic enhancement in the complexity and biomimicry of today's engineering living tissues and organs. A new era is ahead of us in which therapeutic and pharmaceutical application of tissue

engineering will take center stage and replace conventional medicine and drug therapy.

Introduction

Each year, millions of people suffer from variety of diseases that could be aided from therapies such as organ transplantation. However, despite the widespread need from transplantable tissues, many patients die while waiting for donor organs. It is from this need the field of tissue engineering has emerged. Tissue engineering is an interdisciplinary field that involves the use of biological sciences and engineering to develop tissue that restore, maintain or enhance tissue function.

Tissue engineering is readily grasped and has a high intrinsic appeal to scientists, clinicians, investors, and media over conventional drug therapy because it can provide a permanent solution to the problem of organ failure.

Tissue Engineering: The Discovery of the 21st Century

In general, there are three main approaches of tissue engineering; (1) to use isolated cells or cell substitutes; (2) to use acellular biomaterials capable of inducing tissue regeneration and; (3) and to use a combination of cells and material (scaffold), Figure 1.

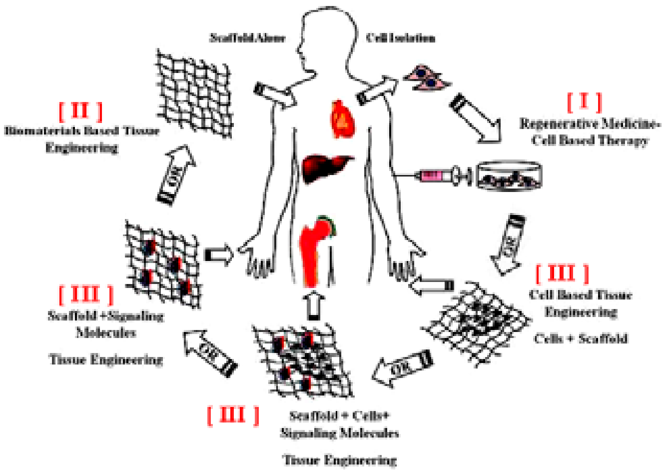

Figure 1. Regenerative Medicine and available approaches of Tissue Engineering

Despite significant advances in tissue engineering which have resulted in successful engineering of organs such as bone (Figures 2, 3); skin and cartilage, there are a number of challenges that remain in making off-the-shelf tissue engineering products.

Figure 2. Engineering bone in vitro using bone marrow mesenchymal stem and PLG (biodegradable polymer); (a) Bone marrow mesenchymal stem cells (BMSCs); (b) BMSCs in colonies seeded on PLG; (c) Bone pieces grown in the lab. (*Tissue Engineering Laboratories, Alexandria University*).

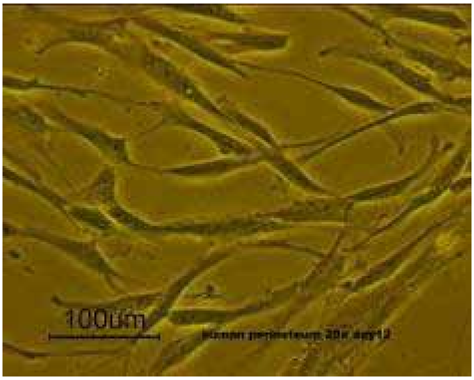

Figure 3. Periodontal tissue engineering utilizing autologous derived periosteal cells seeded onto gelatin/β-Tricalcium phosphate sponge: (a) Periodontal defects in upper right quadrant before treatment; (b) Periosteal cell isolation and culturing; (c) Seeding periosteal cells onto gelatin/β-TCP sponges; (d) Post-operative follow-up–5 months. (*Tissue Engineering Laboratories/ Alexandria University*)

These barriers include the lack a renewable source of functional cells that are immunological compatible with the patient. In addition, there is a lack of biomaterials with desired mechanical, chemical and biological properties. The inability to generate large vascularized tissue that can easily integrate into the host's circulating system with architectural complexity of native tissue is also a great challenge ahead of this field.

It's likely that public and medical communities have great expectations on regenerative medicine and tissue engineering although reported clinical trials are still scanty in tissue engineering. With all this in mind, insight from developmental biology, wound healing, cell cycle and aging provide guides to tissue engineering and regenerative medicine as we move ahead in the coming decade.

There is no tissue repair without the cell-the actual architect of the tissue-either recruited from the host or supplied from an external source, until that time, scientists have focused on identifying the molecular components that comprise life with the hope that rigorous characterization of all the parts will lead to understanding of the whole. As a result of sequencing the genomes of multiple organism, including the human, is now clear that there is more to the equation: the whole is truly greater than sum of its parts. Thus biology is shifting away from reductionism towards the development of methods and approaches that deal with 'Biocomplexity'. The challenges here is; to understand how complex cell and tissue behaviors emerge from collective interactions among multiple molecular components at the genomic and proteomic levels and to describe molecular process as integrated hierarchical systems rather than isolated parts.

Biomimetics: The Evolution of the Next Generation of Tissue Engineering

A) Developmental biology

Concepts that are intrinsic for developmental biology are becoming essential for the new generation of tissue engineering: temporal and spatial signaling, niche development, physical regulatory factors. Scientists agreed that we need to integrate more developmental and systems biology into the design of the scaffold and bioreactors as well as information from wound healing and cell cycle in general. Recent advances in the design and implementation of scaffolds and bioreactors demonstrate establishing systems as high fidelity in vitro niches for controlling cells function and tissue assembly and function.

Biomimetic approach to tissue engineering or emulation of some aspects of normal tissue development and remodeling structures the feature of the next generation of the field. Bridging the gaps between developmental biology and tissue engineering involves few, yet essential areas for further investigation. First, establish in-vivo load and deformation histories that native tissues experiences during activities of daily life. Second, establish the safety factors and relevant biomechanical failure for a wide range of normal activities. Third: understand the details of macro-and microstructure/ function relationships of normal native tissue. Fourth, determine the mechano-signal transduction processes humoral, neurological, chemical, and physical in cells that maintain tissue homeostasis. Fifth, develop computational models that incorporate an accurate description of anatomic form at various hierarchical levels.

While the first decade tissue engineering focused primarily on the development of enabling technologies needed to create tissue engineering constructs from cells, hormonal factors, and synthetic matrices, the second decade tissue engineering describes the road map to employ and assess the mechanical end function qualities of the construct. In order to broadly define function it would seem important to understand the range of normal before injury. Given the importance of stem cell, there was agreement that natal and postnatal development must be fully recapitulated in tissue engineering.

B) Developmental Engineering

Recent advances in developmental biology, system biology and network science are converging to poise the field of tissue engineering into imitate to some degree natural mechanisms that control cell fate and differentiation. This new paradigm focuses on design and manufacturing of cell-based products. It incorporates on its process design some accepted rules and direction e.g., path-dependence robustness, modularity, and semi-autonomy of intermediate tissue form, that all appears, sequentially during tissue development.

Path-dependence means that each developmental stage depends on the previous ones and optimal conditions are self-established by the process. An example is endochondral ossification, the developmental process for the formation of bone through gradual replacement by bone. While the first decade tissue engineering favored intramembranous ossification, the one-stage direct osteogenic differentiation of mesenchymal stem cells, the second decade tissue engineering through the attention to developing cartilage itself could considered as self-designed scaffold that is simultaneously osteogenic and angiogenic.

Robustness analysis of the empirical concepts of developmental biology and their significance in process design. In other words empirical concepts established from the studies of developmental phenomena are strikingly related to engineering concepts of robust process design. To achieve this goal, tissue engineering next generation will have to address process stability and product reproducibility. It should include validation, well controlled manufacturing process with controlled and product release specifications that provide reasonable assurance of safety and effectiveness.

Modularity or modular assemblies in sequential sub-processes. It involved apparent need to emulate the gradual progression of tissue variable such as tissue size, cell differentiation and cell organization that occurs in vivo, such a process could start with the placement of stem cells in small scaffolds, increasing scaffold size at an intermediate stage when the cells have started but not yet completed their differentiation. In the final stage, the scaffold is increased to its final size. Gradual increase of bio-artificial tissue size has been introduced in tissue engineering methods in context of cell-to-cell communication e.g., cell-sheet technology.

The semi-autonomy of inter-mediate tissue forms that appears in multistage tissue development is suggested strongly in the next generation tissue engineering. An example is the induction of the hepatic differentiation and early stages of hepatic morphogenesis that involve generation of hepatoblasts as well as endothelial cells as an intermediate that provide the signals for hepatic development. Similarly, ostoeclasts, that is considered recently as an intermediate stage in a bio-artificial bone that can assure bone remodeling after implantation.

These advances thus open the door to a transition for tissue engineering from substantially empirical endeavor to a technology-based discipline comparable to other branches of engineering and medicine.

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Advances in Rehabilitating Patients with Brain Injury

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Summary

The most common and persistent consequences of acquired brain injury are impaired consciousness, neuropsychological dysfunction, language and speech disorders, and physical and motor impairment. Treatment of these disorders requires highly specialized and carefully timed protocols. Herein, we focus on the role and effectiveness of current protocols, including pharmacological, behavioral, psychotherapeutic and technological intervention. Current clinical data indicate that it is possible to treat organic functional deficits with new rehabilitation techniques. We review two functional rehabilitation models, the Prosthetic Method and the Combined Method TCM, and their diverse methodology and results. The Prosthetic Method is cognitive, orthotic, or assistive technology, a compensatory method of neurorehabilitation. Compensatory methods are cognitive orthopedics, which neither rehabilitate nor facilitate functional recovery. TCM is a methodological engineering process, combining knowledge on the intact and non-intact functional brain with cognition, emotion, behavior and neuropharmacology, resulting in cerebral functional reorganization and involving new methods for effective neuropsychological and physical rehabilitation.

Traumatic Brain Injury

Traumatic brain injury is common, affecting all age groups and generally more men than women. The functional consequences range from mild to moderate sequelae to death. Traumatic brain injury (TBI) is the cause for one third of all deaths in civilized countries. The most common causes of TBI are traffic accidents, job, sports and leisure activity accidents, collisions by road vehicles, and acts of violence. The age range most frequently affected is between 15 and 24 years of age. TBI often produces physical and neuropsychological sequelae including deficits in memory function, orientation, reasoning, executive functioning, and emotional, motor and social behavior. (Leon-Carrion, Dominguez-Morales, Barroso, and Murillo, 2006). In most cases, these deficits have a significant effect on social and family relationships (Leon-Carrion and Ramos, 2003).

The sequelae of patients with TBI will depend on whether they stem from primary brain damage, secondary brain damage or both. Primary brain damage occurs at the moment of the injury, whereas secondary damage is an evolution or complication of the primary damage. Primary damage in neuroimages (or x-rays) includes fractures, contusions, lacerations, diffuse axonal damage and intracranial hemorrhages (Muñoz-Sanchez, Murillo-Cabezas, Cayuela, et al. 2009). Secondary brain damage includes cerebral edema, hypoxia or ischemia, increased intracranial pressure and infections. Any individual involved in the treatment of patients with TBI should have extensive knowledge of these kinds of injuries. Both MRI and PET provide images that are of fundamental value for designing treatment during the acute and post-acute phase by helping monitor the efficacy of these treatments.

Functional and Structural Consequences of TBI

The human brain—highly complex and responsible for human behaviour and cognition—is very vulnerable to damage and blows to the head, the consequences and treatment of which are equally complicated. Sometimes mild brain injury can lead to serious problems, whereas a severe TBI can be overcome, with the patient returning to a normal life with only minor deficits or changes in personality.

During the acute phase of any blow to the head, the medical attention should be immediate, primarily to save the person's life and avoid secondary damage which could affect the patient's recovery (see Figure 1).

The neuropsychological and physical sequelae stem from primary and secondary sequelae. Since primary damage is difficult to avoid once it is

Figure 1. Early identification and treatment of intracranial haematomas in patients sustaining traumatic brain injury is a fundamental part of the initial diagnosis and treatment of these individuals. At present, only hospitals equipped with a radiology department could carry out neuroimaging studies on these patients upon their arrival. The InfrascannerTM NIRS device (InfraScan, Inc., Philadelphia, PA) used for haematoma detection, uses light guides touching the scalp to calculate optical density in brain regions. The exam covers the most common locations for traumatic haematomas, usually lasting three minutes. The handheld near-infrared (NIR) Infrascanner evidences a high sensitivity and a high specificity to detect intra and extraxial hemorrhagic haematomas and most importantly, it is able to detect small haematomas (>25mm) and detect them within the following 24 hours.

produced, then avoiding secondary damage should be of utmost importance from the onset. Hence, quick and efficient primary attention would help avoid complications which could result in sequelae affecting a person's independence is daily life activities and relationships.

In the post-acute phase, it is important to correctly define the sequelae and deficits suffered by the patient as a result of his or her TBI. The intervention of neuropsychologists is fundamental and essential to this undertaking. Equally important in this task are neuroimages of the patients, providing a guide on the possible functional deficits which a patient could have. These neuroimages should be read, interpreted and reported on by specialized person. The readings should be meticulous, so as to provide correct detailed information. All patients should receive a neurological assessment, during both the acute and post-acute phase, as well as a specialized neuropsychological test. These studies are essential, particularly when changes in the clinical state of the patient are observed. These changes could be due to the development of obstructive hydrocephalus, an intracerebral hemorrhage, hyponatremia, hypopituitarism, etc.

Neuroimaging in TBI

Brain injury produces changes in cortical and subcortical cerebral organization. This alters the composition of functional cerebral networks and impairs the connection between intact and damaged zones of the brain. The mechanisms which produce behavioral sequelae are diverse. During the acute phase, there is an excess of neural activation; in the post-acute phase, we find depression, functional hypoactivity or neural hypoactivity. A brain injury or lesion can affect psychological functions temporarily or permanently, producing functional activity disorders which could be reversible, partially reversible, or irreversible (Leon-Carrion, Martin-Rodriguez, Damas, Barroso, et al. 2008).

The correlation of neuroimages with the neuropsychological and physical status of the patient helps determine which clinical changes he or she is undergoing. These neuroimages are also important in assessing whether ischemic lesions are acute or chronic. Currently, sequences of MRIs are capable of showing the age of the brain injury with certain precision, in other words, when it was produced, and whether it is recent or chronic. The use of neuroimages combined with the neuropsychological state of the patient may avoid having to apply more invasive techniques, such as a lumbar puncture, making them useful as a first option. Moreover, we now can make use of neuroimaging techniques in real time, which could be used both in the operating room and in research on functional brain processes.

Plasticity, Reorganization, and Regeneration after TBI Through Neurorehabilitation

The reversibility or irreversibility of functional damage due to TBI depends on three factors: the magnitude of the associated brain lesion, the functional relevance of the cerebral network in the damaged zone, and the genetic, idiosyncratic and personal capacity for recovery of the individual's central nervous system (Martin-Rodriguez and Leon-Carrion,

Figure 2. Recording of cerebral activity in the prefrontal dorsolateral cortex of a patient with TBI while is doing the 'Tower of Hanoi/Sevilla' computerized neuropsychological task (www.neurobirds.com). This recording studies in vivo his executive and problem solving capacities.

2010). Rehabilitation programs aim to create, reestablish or rebuild the psychophysiological structures implicated in the deteriorated function by activating intact cerebral structures and circuits or facilitating new connections. The ultimate goal is to try to rehabilitate the function or help it return to its previous level of functioning. Neuropsychological rehabilitation applies specific systematic training to the deteriorated or lost function, utilizing cognitive, behavioral, motor, executive and language exercises. Neuropsychological and motor exercises modify cerebral circuits and biochemistry both permanently and differentially. These modifications are made via the different psychobiological experiences produced during the rehabilitation process (Leon-Carrion, Martin-Rodriguez, Damas, et al. 2008; Leon-Carrion, Martin-Rodriguez, Damas, et al. 2009).

The three principles of neurorehabilitation are plasticity, reorganization, and regeneration of the central nervous system. Neurorehabilitation leads to plastic changes in the central nervous system, including an increase in the rate of protein synthesis and a controlled and precise increase in the

Figure 3. Patient performing a biofeedback exercise, a treatment for his facial muscle paralysis, at the Center for Brain Injury Rehabilitation--CRECER (www.neurocrecer.es).

number of proteins in the cortex. This produces a biochemical cascade which can modify neural circuit responses and connectivity. The human brain is plastic and has a strong capacity for reorganization, including spontaneous reorganization. Spontaneous recovery, however, is limited. Programmed systematic training is needed to activate the mechanisms underlying cerebral plasticity.

Cognitive and behavioral exercises promote dendritic growth simultaneous to the recovery of behavioral or cognitive abilities; this occurs during the neuropsychological rehabilitation process (Leon-Carrion, von Wild and Zitney, 2006). The studies carried out by our team showed that spontaneous recovery did not occur after four months post-stroke. After the sixth or seventh month post-cranial trauma, spontaneous recovery did not exist. The recovery of cognitive or emotional functions was possible at this point in time through a rehabilitative effort requiring specific neuropsychological treatment (Leon-Carrion, 1997).

The Prosthetic Method of Neurorehabilitation

Pessimism towards cognitive rehabilitation following brain injury has led to the predominance of prosthetic rehabilitation in journals and publication, with almost total exclusion of the rehabilitative approach to treatment and research. Herein, we focus on the two models of cognitive functional rehabilitation and their diverse methodologies and results: The Prosthetic Model and the Combined Method (TCM).

Compensatory cognitive rehabilitation is external, involving prosthetic aids, such as the use of agendas, notebooks, pagers, mobile phones, portable computers, etc. Although it has received positive recommendations (Cicerone et al., 2000), no evidence exists that external memory aids result in meaningful improvement of core cognitive skills. During the 1970s and 80s, restoring organic memory and cognitive disorders was seen as an impossible goal. Most rehabilitation techniques were based on the cognitive psychology of memory with little or no cerebral basis. A study in the early 1990s tried to discover if any of these cognitive techniques were effective in memory recovery. Results showed that only one out of five approaches (Visual Mnemonics) may be useful for patients with memory disorders. These results were not very encouraging for professionals dedicated to organic memory disorder. This pessimism, together with the difficulties found in rehabilitation, gave rise to the strengthening of the prosthetic method of cognitive rehabilitation.

Proponents of the prosthetic method of cognitive rehabilitation recommend the application of compensatory cognitive strategies, adapted to groups of patients and individuals. This method is based on the belief that neurocognitive functions (memory, reasoning, attention executive functions, etc.) are not recoverable, or that recuperation is so limited that the patient cannot lead an independent life. Hence, the best solution is to train the patient to use external aids to carry out daily activities. Some authors have noted the limitations of this method. The orthotic method or assistive technology can be effective for a limited group of patients and circumstances. The aforementioned devices have significant shortcomings that reduce their appropriateness for many patients. In most cases, they are unsuitable for delivering complex or lengthy procedural guidance, and their capacity is limited.

Furthermore, compensatory cognitive strategies proposed by the prosthetic method (diaries, programmed watches, etc.) neither rehabilitate nor facilitate the recovery of cognition. These methods impede rehabilitation efforts by preventing the patient from using his/her own resources and efforts for memory recovery, indispensable for recuperation. These should be used when all other treatments fail, in emergencies or where rehabilitation is impossible. Compensatory methods are cognitive orthopedic.

The Combined Method (TCM) of Neurorehabilitation

Evidence of the worthiness of cognitive rehabilitation has been documented. Cicerone reviewed 23 Class I articles, noting that 17 provided positive evidence for the effectiveness of cognitive rehabilitation and 6 reported generalized improvement of functional abilities. He concluded that the available evidence on the effectiveness of cognitive rehabilitation should enable clinicians to advocate the most realistic and effective treatment for individuals who require neurocognitive rehabilitation.

TCM is a methodological engineering process designed for the rehabilitation of patients with acquired brain injury (ABI). It combines knowledge on the intact and non-intact functional brain with cognition, emotion, behavior and neuropharmacology. This combination of neuropsychological and pharmacological strategies is aimed at generating functional cerebral reorganization, psychological coherence and social coherence in patients with ABI (Leon-Carrion, Dominguez-Roldan, Murillo-Cabezas, et al, 2000).

We studied ABI patients to assess functional recovery of cognitive, behavioral and motor deficits two years after onset. Patients received TCM treatment for a mean period of 7.57 months, with the following results: overall recovery of 64.74%; cognitive functionality increase to 86.91%; motor and physical functionality reached 84.41%; 100% functionality in some patients in certain areas at the end of their treatment.

The Neuropsychological Principles of the Combined Method

1. For the brain to work, it needs oxygen and sugar. These are supplied via continuous blood flow. The cerebral zones activated by a cognitive process are more active than those requiring oxygen and glucose. If a brain injury impedes

blood from reaching these zones, the different cognitive processes cannot be carried out.

2. Cognition is a broad concept. Even a specific cognitive function can be expressed as a network of related functional subsets. Moreover, cognitive disorders after brain injury can be varied, with different memory disorders be found in the same patient.
3. Each cognitive disorder after brain injury should be approached with its specific techniques. This should be done under the general context of rehabilitation.
4. Cognitive rehabilitation should be tailor-made for each patient.
5. It should take into account the characteristics and idiosyncrasies of specific kinds of cognitive disorders and the motor deficiencies of each patient.
6. The patient´s effort in performing cognitive exercises is a fundamental part of TCM rehabilitation process. Without this effort, there is insufficient cerebral activity to revitalize the physiological and neural activity needed in the areas of the brain associated with cognition.
7. The rehabilitation of cognition through the Combined Method is based on the same principles as physical therapy. First, resolve the physical injury in order to recover functionality. Second, apply neuropsychological training to exercise the impaired cognitive functions.
8. Cognitive neurorehabilitation is a complex process. It requires well-trained neuropsychologists, experienced in the evaluation and rehabilitation of diverse cognitive disorders.

TCM cognitive strategies follow a general scientific logic similar to that of physical therapy. The latter is based on two principals:

1. Physical injury to the brain causes functional impairment. In order to recover functionality, we must first resolve the underlying basis of this impairment.
2. We must exercise the function in order to recover it. These principles apply to the cognitive therapy used in TCM.

Firstly, brain tissue would have to recover and maintain its metabolic activity. This is achieved through normalization of blood flow in specific areas related to cognition. Secondly, neuropsychological training would be applied to exercise impaired cognitive functions.

Europharmacology is an essential part of TCM. (Table 1) highlights the use of certain drugs to enhance different aspects of attention, language and memory.

Table 1. Some of the drugs used to enhance different aspects of attention, language and memory.

Attention	Memory	Language
Amantadine	Bromocriptine	Amphetamine
Amitriptyline	Choline	Bromocriptine
Amphetamine	Clonidine	Carbidopa/levodopa
Clonidine	Citicholine	Tricyclic antidepressants
Desipramine	D-Amphetamine	
Methylphenidate	Ginkgo biloba	
Pemoline	Nimodipine	
Protriptyline	Selegiline	

The Prognosis and Course of Cognitive Neurorehabilitation

Cognitive disorders can be treated, and that it is possible to place patients at near normalcy and even at normalcy. Patients with serious memory deterioration that severely affected their daily activities reported improved, less dysfunctional memory function after treatment, increasing their independence and personal autonomy. As previously noted, these types of patients usually have more than one cognitive problem, making it necessary to add the rehabilitation periods together for both/all of them. For example, TBI patients with diffuse axonal damage usually have at least two or three cognitive deficits.

Overall, we can say that a combined intensive, holistic and multi-disciplinary treatment requires at least 150 hours of cognitive rehabilitation, in addition to the hours the patient needs for physical, emotional, and speech rehabilitation. No less than 400 hours of rehabilitation is needed for a TBI patient with several cognitive impairments to achieve a level of normalcy.

Cognitive rehabilitation treatment requires time and continuity. The effectiveness of TCM depends on time, continuity and the intensity of cognitive training sessions. To reach over 70% of memory, patients in our study required 68.2 1/hr sessions for short-term memory deficits, 67.1 1/hr sessions for long-term memory deficits, and 79.2 hours needed for planning. The results also show that the recovery process for organic cognitive disorders is irregular, with ups and downs. At times (not more than 15%), treatment effects seems to recede. This could be temporary—a month later, recuperation continues. If a downtrend is over 15%, the underlying cause must be found

Figure 4. Two therapists aid a patient with exercises designed to treat his inability to remain standing and recover the bipedal position.

Table 2. Cognitive rehabilitation treatment

Disorders	Admission	Discharge	Hrs/Session
Long-term memory	4.20	7.70	67.1
Short-term memory	3.80	7.40	68.2
Orientation	7.50	9.40	80.2
Calculation	4.30	6.80	58.6
Attention	4.50	7.00	65.2
Automatisms	4.50	7.00	70.9
Mental Control	3.20	7.20	47.2
Planning	4.30	7.50	79.2

immediately. Our data indicate that the rehabilitation process must continue until consolidation of all progress is achieved.

Mean scores on scale of 1–10 from admission to discharge for rehabilitation of cognitive disorders and hours needed to achieve goal of 70% normalcy. Everyday cognitive functioning was clinically scored on a scale of 1–10. Results from neuropsychological assessment at admission were taken as baseline. These were assigned scores as follows: one to two subjects with severe impairment (normalcy at 10–20%), seven subjects exhibiting good response (normalcy at 70%), and ten subjects with statistical or clinical normalcy (100%).

Acknowledgements

To the Center for Brain Injury Rehabilitation (CRECER) in Seville for providing grant permission for figures used in this chapter.

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Membranes for Artificial Organs Applied to Haemodialysis

Jörg Vienken

Summary

Since more than 50 years, membranes keep kidney patients alive. Exponentially rising patient numbers currently stimulate further improvements in routine dialysis therapy. With high flux membranes (UF-Coefficient >20 ml/h·mmHg), a large variety of possibly toxic molecules can be removed from the patients blood by convective transport and solvent drag. Safety features with regard to endotoxin contamination of dialysis fluid and substitution fluids can be overcome by endotoxin-adsorbing polymers such as polysulfone. Future membrane application research will focus on the interplay between dialysis machine and membrane.

Introduction

The treatment of chronic kidney failure by haemodialysis is by far the largest realm of membranes in medical application. When Thomas Graham (1805-1869) described the basic principles of dialysis in Glasgow and termed the name dialyser for the first time (Graham, 1854), he could not foresee that about 160 years later, about 1,700,000 patients with chronic kidney disease owe their lives to this therapy (Moeller, 2010). These figures still follow an exponential rise with an annual increase of currently 6–7% worldwide.

The standard therapy of chronic kidney patients refers to three about four-hour long haemodialysis treatments per week. This significant, but life-saving, burden to the patient has been brought to perfection in such a way, that quality of life and survival of dialysis patients has been steadily improved as shown by statistics from the Japaneze Society for Dialysis Therapy (JSDT). In Japan, currently more than 67,000 kidney patients are treated by dialysis for already longer than 10 years, whereby the longest history of dialysis could be traced to a patient with a dialysis history of 39 years and eight months (Nakai, 2009). Comparable data can be obtained from other countries in the Western hemisphere. The situation in developing countries has not yet reached this level, but conditions are steadily improving. The help and support of local governments, NGOs and dialysis provider companies provides better healthcare for dialysis patients which can be documented by increasing patient numbers in the third world.

Therapy of Chronic Kidney Patients

Chronic dialysis patients suffer from a nearly complete failure of their kidneys. This includes the kidneys filtering capacity for uremic toxins, the maintenance of homeostasis and the secretory function for hormones, such as erythropoietin (EPO). Current therapeutic maneuvers with the Artificial Kidney aim to remove uremic toxins (Vanholder, 2003) via extracorporeal blood circuits. By means of such a circuit, uremic toxins are filtered across capillary membranes and then removed by a dialysis fluid (Figure 1). The dialysis machine which is connected to the artificial kidney through tubing systems controls blood flow and dialysis fluid flow by peristaltic pumps, blood temperature and—pressure by specific sensors and the patient´s electrolyte balance by specific control features. The therapy with the artificial kidney, however, only replaces the functions of the glomerulus, the filtering unit of the kidney. To date, the functions of the kidney tubulus cannot yet be replaced by artificial means.

What are the general typical features of the key elements of the dialysis system, the Artificial Kidney and the filtering dialysis membrane?

Artificial Kidneys (dialysers) are small medical devices which allow blood purification by filtering blood through capillary membranes. Dialysers contain a bundle of about 10,000 capillary membranes. Membrane function is located in the wall of the hollow fibres. During dialysis treatment, blood

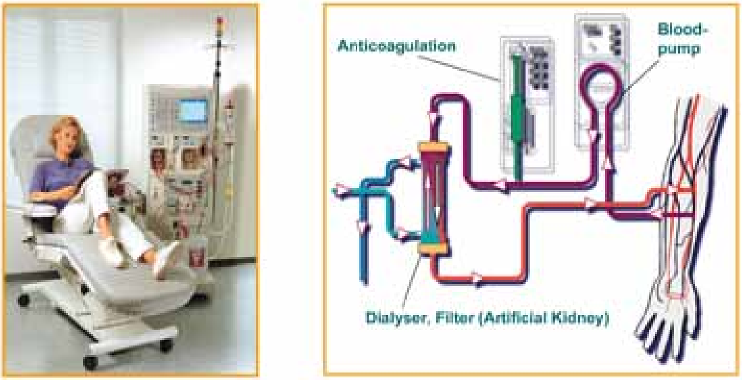
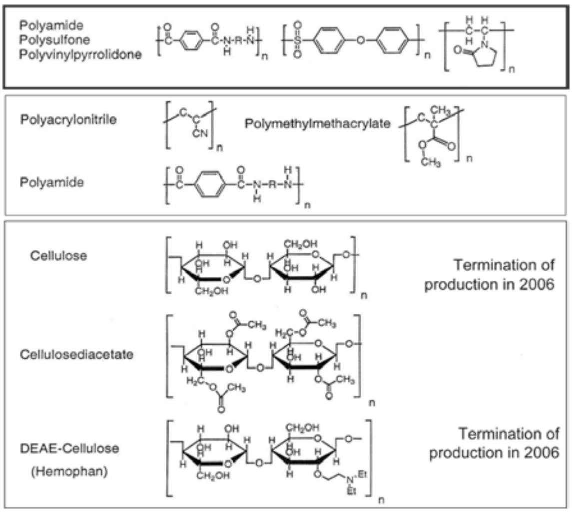


Figure 1. Dialysis patients regularly spent four hours attached to a dialysis machine three times a week (left). Blood is guided from the forearm vein to the artificial kidney with the help of a peristaltic pump. Anticoagulation is performed upfront the dialyser by a continuous infusion of heparin. After having passed the dialyser, blood returns directly to the patient. Filtered toxins and ultrafiltered water are removed with the help of an isotonic dialysis fluid.

Table 1. Chemical formula of polymers used for the fabrication of dialysis membranes. The majority of dialysis membranes is made from the synthetic polymers PSu-polysulfone, PA – polyamide.



perfuses through the capillaries and its uremic toxins are filtered across the wall by means of a transmembrane pressure. Removal of toxins is achieved by an aqueous isotonic dialysis fluid streaming in counter current direction to blood through the intercapillary space.

Membranes for dialysis are made today mostly from either pure synthetic polymers, such as polysulfone (PSu), polymethylmethacrylate (PMMA), polyacrylonitrile (PAN) or polyamide (PA). Cellulosic membranes, that dominated the dialysis market for decades, are not produced any more with the exception of cellulose acetate derivatives. Some synthetic membranes are modified with polyvinylpyrrolidone (PVP). Blending with PVP allows to vary the water repellent properties of otherwise hydrophobic polymers to partly hydrophilic.

PAN-polyacrylonitrile, PMMA-polymethylmethacrylate. The formerly dominating cellulosic membranes, e.g. Cuprophan® (unmodified cellulose) and Hemophan® (etherifed cellulose are not manufactured any more. A typical dialyser (Figure 2) contains between two and three kilometres of

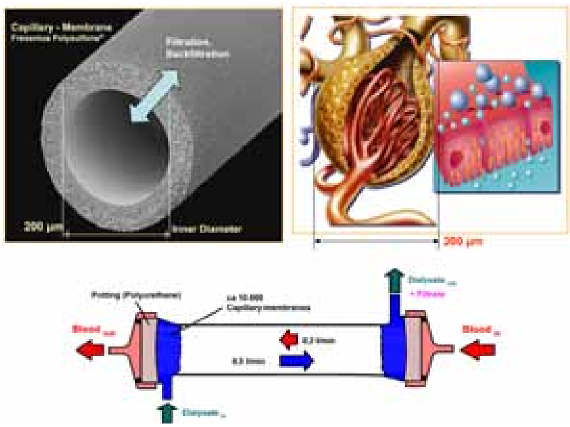


Figure 2. The artificial kidney (lower panel) contains about 10,000 capillary membranes. Their dimension is surprisingly small. The inner diameter of the lumen is in the range of 200 μm, the wall representing the membrane about 40 μm thick. The membrane, here an micrograph of a capillary membrane made from polysulfone, is the filtering unit of the artificial kidney like the glomerulus (right) represents the filtering unit of the natural kidney. It is interesting to note, that the diameter of the glomerulus fits exactly into the inner lumen of the capillary membrane.

capillary membranes. This figure allows us to estimate the current annual need for capillary membranes which adds to more than 500 million kilometres worldwide.

It might satisfy the curiosity of the interested reader to have a detailed look at the dimensions of capillary membranes. They are spun like textile fibres through a circular orifice. A non-solvent solution or air is guided through the core of the orifice in order to maintain the hollow fibre´s shape. The core diameter of the orifice is kept in the low micrometer range such that a final inner diameter of about 200µm can be achieved for standard capillary membranes. When blood is filtered from the inner lumen of the capillary to the outer space, toxins and water have to pass a membrane wall whose thickness is typically in the range of 40µm. These dimensions prove the extraordinary skill of engineers and the technological perfection of manufacturers who guarantee quality and performance for a device which saves the lives of so many dialysis patients.

Performance Requirements for Dialysis Membranes

Current dialysis treatments are applied to remove water and uremic toxins. Consequently, membrane permeability and performance are important parameters for manufacturers, physicians and patients, because they determine therapy efficiency, treatment time and patient survival.

In the early days of membrane application, low flux membranes, characterized by an ultrafiltration coefficient UFC of less than 10 ml/h·mmHg, have been regularly applied. Their application was finally limited for two reasons: (1) Increased transmembrane pressures TMP are needed to obtain large ultrafiltration rates. Thus, these membrane types could not be used for modern treatment modes, such as hemo*dia*filtration HDF. In HDF high ultrafiltration rates are applied in order to provide a solvent drag for the transport and removal of large molecules. In addition, the application of high TMPs, e.g., above 300 mmHg, could provoke damage to red blood cells and stimulate platelet activation; (2) Low flux membranes exhibit a rather low molecular weight cut-off, i.e. molecules with a molecular weight above 10,000 are retained. Nephrologists, however, are currently interested in removing small proteins, such as ß-microglobulin (Mol.-Weight: 11.818), which is only possible by the use of high flux membranes. High flux membranes with an UF-coefficient >20ml/h·mmHg achieve a reasonable ultrafiltration by means of rather decent TMPs .

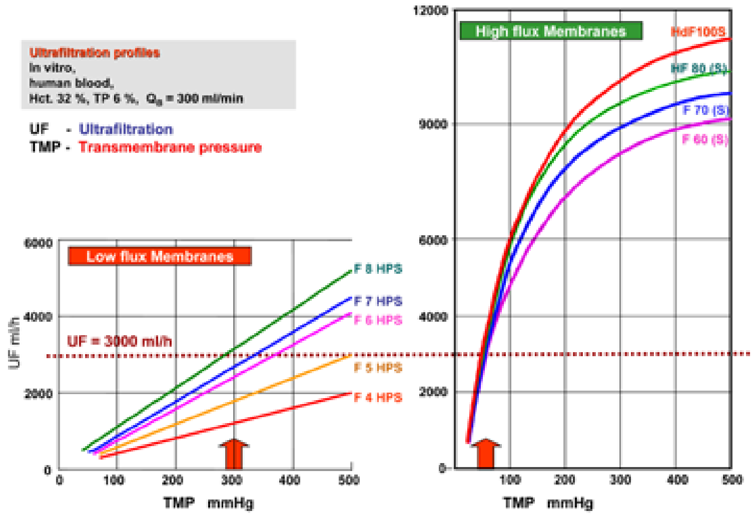


Figure 3. Ultrafiltration performance for low- and high flux dialysers. In order to obtain an ultrafiltration volume of about 3,000ml a transmembrane pressure above 300 mmHg has to be applied for low flux dialysers (red arrow). To obtain the same ultrafiltration volume with high flux dialysers, only a TMP of about 50 mmHg is necessary. Different lines represent dialysers with polysulfone membranes of different surface areas.

Convective Transport (CT) that favours the removal of larger molecules, can be defined as CT = SC x UF where SC stands for the sieving coefficient of the membrane and UF for the applied ultrafiltration rate. In parallel to their higher UF-coefficients, high flux membranes show larger sieving coefficients for small proteins (Figure 4). Modern membrane manufacturing technologies are able to produce tailor-made membranes according to the requirements of the nephrologist and shift the sieving coefficient curve towards larger molecular weights.

Despite the notion that proteomic analysis of ultrafiltrates from dialysis was unable to identify a single, but specific culprit molecule, which is responsible for kidney failure (Weissinger, 2004), current treatment philosophies target the removal of a large variety of molecules for the therapy of kidney failure. High flux membranes are considered the ideal tools for this purpose and have, thus, been recommended by the authors of the European Best Practice Guidelines for Haemodialysis (EBPG, 2002).

Facts mentioned above have led to an increase in the application of high flux membranes in the world. In recent years, they have replaced their low

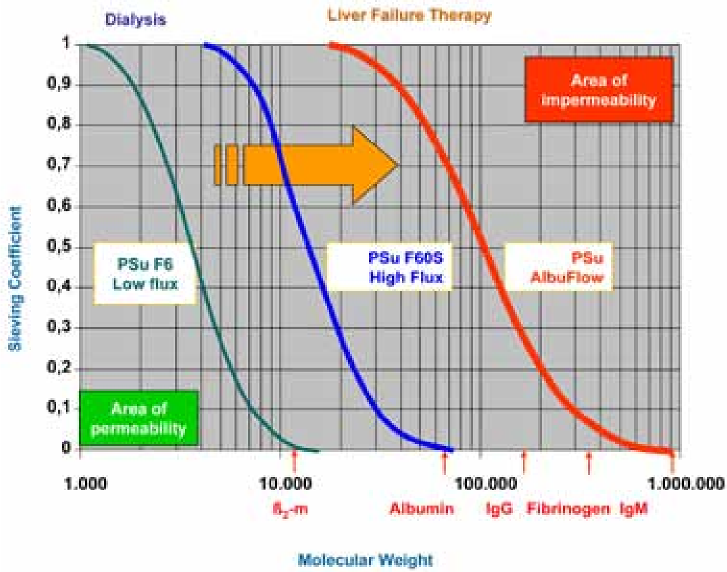


Figure 4. Sieving coefficient curve for low- and high flux polysulfone dialysis membranes. The sieving coefficient represents the percentage of passage for a molecule with a given molecular weight.
Molecules present at the left hand side of the sieving coefficient curve may pass the membranes, whereas the membrane is impermeable for molecules located on the right hand side of the curve. By modifying the membrane formation process, it is possible to shift the SC-curve to higher molecular weights and fabricate membranes of higher permeability. By this means, high flux membranes or even membranes for liver failure therapies are obtained.

flux counter parts in many applications. Currently, high flux membranes in haemodialysis cover a 65% worldwide market share.

The biocompatibility of dialysers, particularly that of its membrane, is one of the main criteria for choosing a particular dialyser. In the landmark publication on biocompatibility a definition was elaborated by the participants of the 'Consensus Conference on Biocompatibility' held in 1993, as '..the ability of a material, device or system to perform without a significant host response in a specific application' (Gurland.1994). The addition of the term 'significant made the definition less strict than earlier ones, which demanded the absence of all host responses, and reflects the realisation that all foreign materials available at the present induce some kind of reaction in the host. In renal replacement therapy, interactions between blood and the artificial surface, such as the dialysis membrane, are especially important due to the chronic character of the treatment.

The contact of blood with artificial surfaces initiates the activation of a series of pathways, such as the clotting cascade or the complement system. Further, immune cells, like neutrophils and monocytes, and platelets are activated either by products of the complement system or the clotting cascades, or by direct membrane contact. It has to be noted that the membrane represents the largest foreign surface in the extracorporeal blood circuit in haemodialysis. Consequently, huge efforts have been undertaken to improve blood compatibility of dialyser membranes or to reduce its clinical side effects (Vienken, 2010). Current membrane polymers used for dialysis exhibit a rather low state of interaction with the least effects found for polysulfone blends.

Requested Membrane Features for Routine Hemodialysis

'Better safe than sorry'. This slogan is currently used to describe the potential risks of genetic engineering also addresses possible threats in dialysis care where safety issues are of central importance. This risk relates to the fact that dialysis membranes are not a 'one-way-street' . Toxins from the patient´s plasma are transported across the membrane into the capillary bed and any contaminant, originating from the dialysis fluid,

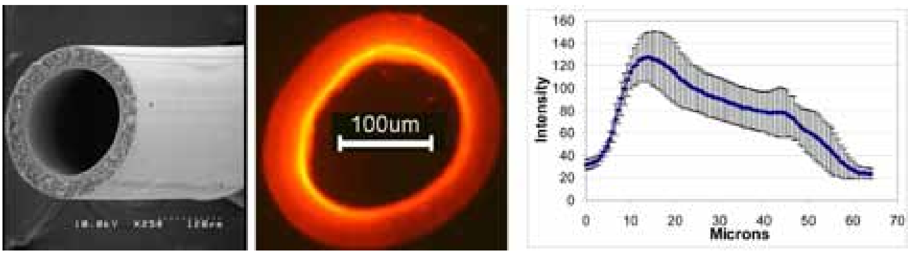


Figure 5. Polysulfone membranes have a high adsorptive capacity for endotoxins. In this experiment endotoxins labelled with fluorescent dyes are exposed to the intercapillary space of the dialyser and the passage from outside the capillary membrane to the lumen is studied. PSu-membranes adsorb endotoxins in their bulk as shown by the light ring around the lumen of the capillary and thus offer effective safety features for the patient. (Modified after Henrie 2008)

may enter the bloodstream across the membrane from the reverse side via backfiltration. Membrane pore size dimensions in dialysis are in a range that allow for this transfer (Vanholder, 1992; Hoenich, 2010). Among the transferrable water contaminants are heavy metal ions, organic compounds from disinfection or cleansing processes, like chloramine or acetone (Ismail, 1996; ISO 13959), residuals from the water tubing systems and most importantly bacterial products such as endotoxins and exotoxins (Berland, 1995). Organic and anorganic contaminants can be removed from dialysis fluids prior to entering the final dialysis system by adequately designed absorber cartridges and reverse osmosis units (ISO 26722, 2009). Bacterial contamination of dialysis fluids can be avoided with the help of polysulfone dialysis membranes. Detailed experiments have shown that the passage of water across a polysulfone capillary membrane leads to a reduction of the endotoxin burden by six orders of magnitude and can be kept below detection limit of the limulus assay (Weber, 2000). Precise analyses of the mechanism behind prove that endotoxins are adsorbed in the inner bulk structure of the capillary wall (Figure 5), whereby the benzene rings within the polysulfone molecule can be made responsible for such an interaction (Henrie, 2008).

Taken together, serious and intensive efforts have to be undertaken in order to keep water quality for haemodialysis at such a high level that long term clinical sequaelae can be avoided in chronic haemodialysis patients (ISO11663. 2009).

Dialysers must be sterilised before clinical use. Common sterilisation methods as employed by dialyser manufacturers are generally based on the use of ethylene oxide, ETO, irradiation by g- or ß-rays, E-beam or heat/steam. In 2009, 9,6% of dialysers have been sterilised by ETO, 36,6% by steam and 53,8% of dialysers worldwide have been sterilized by any kind of irradiation). Only the effect of the sterilisation procedure on the dialyser membrane is truly limiting, as other filter components can generally be exchanged to accommodate a particulate sterilisation method. Not all dialyser membranes can be sterilised by each of the procedures indicated. Typical grounds are chemical residues, discoloration, membrane degradation and formation and release of sterilisation by-products. As a consequence, the currently mostly applied sterilisation procedures for membranes in medical devices are E-beam and steam, because these procedures guarantee low amount of residuals due to the rinsing processes in steam sterilisation and low mechanical and thermal stress for polymers in the case of E-beam sterilisation (Uhlenbusch-Körwer 2004).

Conclusion

Membranes in dialysis are high tech products. Their geometry and performance together with their biocompatibility can be adapted to the needs of kidney patients. This notion is in part the basis of the success of dialysis therapies in keeping patients alive.

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Gknowmix.com: A Gateway to Genomic Healthcare

Maritha J. Kotze

This paper explains the benefits of a new, open innovation, medical model designed to bridge the gap between molecular genetics and clinical practice. Genomic complexities are encoded in the system, and presented to users in the form of an interactive website, Gknowmix.com. The development of the Gknowmix software started out as a pilot project for a business model that can be duplicated and re-used by other scientists working in close collaboration with clinicians. The success of the system relies on a unified vision that will extend beyond the leadership of one individual and be carried forward by any number of participating scientists, genetic counsellors and clinicians without limit. In the initial stages of development and growth the two founders strive to interact in positive ways with all stakeholders and implement the changes required to transform molecular genetics from a primarily laboratory-based science to an information and knowledge management discipline.

Introduction

Genetic testing is used increasingly to determine the likelihood (or risk) of disease development or recurrence, and to convert genetic knowledge into preventative and treatment-based action to lower the risk. How our bodies react to certain factors in the environment such as diet (nutrigenetics) and medical treatment (pharmacogenetics) has also found expression in our genes. Drug side effects or treatment failure of prescription medication may be due to impaired drug metabolism. Knowledge of relevant metabolic areas or biological pathways where one's genetic make-up may fall short provides the key to mitigating such health risks.

We have dedicated many years to ethically approved research projects that clearly demonstrated how certain genetic tests or 'groups of tests' that include pathology testing can aid in the treatment or prevention of disease. The problem is that many individuals only come under the care of a clinician once they have already fallen ill. Furthermore, there are many complex diseases in which the genetic expression must first be apparent before the clinician can intervene to prescribe the appropriate treatment.

A shift towards preventative medicine in diagnostic practice, rather than a focus on the diagnoses and treatment of disease after its onset (which is the current medical model) is needed to reduce healthcare cost and improve quality of life. A genetically driven disease that has already taken its course in the patient due to an unfavourable environment can be difficult, if not impossible to treat and cure. Some genetic and pathological tests are proven as obvious aids in diagnoses as well as treatment of disease; but this information is not always easily accessible in an enabling form to clinicians and patients.

To overcome many of the above-mentioned obstacles, a range of disease-specific laboratory tests for complex diseases with both an environmental and genetic component have been developed and made available to clinicians via Gknowmix.com. Education of healthcare practitioners is provided through a series of workshops www.genetalk.co.za, questionnaire-based surveys and a distance-learning course on integrative medicine. These include a section on genomic healthcare, which is focused on cardiovascular disease (CVD) as a good example of a major health problem that can be addressed at the gene-diet level.

Pathology supported Genetic Testing: The CVD Model

The CVD multi-gene test (Kotze et al. 2003; Kotze and Thiart 2003) frequently used as an example in our educational materials includes both a biochemical (pathology) and genetic test component, specifically designed to overcome the limitations of each. This approach is based on the knowledge that CVD risk increases as the number of risk factors accumulates and that the identification of genetic subtypes (e.g. familial hypercholesterolaemia, type III hyperlipoproteinaemia, venous thrombosis) is essential to optimize treatment and for preventative strategies. The Cardiovascular genescreen (Table 1) is performed in conjunction with a medical and lifestyle assessment to guide nutritional and/or pharmacological intervention where appropriate.

Table 1. Cardiovascular disease (CVD) genetic screening options based on family history and clinical features. Copyright Gknowmix (Pty) Ltd. © 2007-present.

Genetic Test Information	*Indication of Referral*
Familial hypercholesterolaemia (FH) test LDL receptor gene mutations D154N, G197del, D200G, D206E, C356Y, G361V, V408M, P664L. (population-specific)	High total cholesterol levels (>7.5 mmol/l in adults) and a family history of early-onset (<55 years) coronary heart disease.
Cardiovascular disease (CVD) subtypes • Dyslipidaemia • Hyperhomocysteinaemia • Thrombophilia • Hereditary haemochromatosis	Moderately raised plasma cholesterol levels (<7.5 mmol/l) and/or elevated homocysteine levels, or family history of CVD or venous thrombosis. Cardiomyopathy or diabetes may result from iron overload (hereditary heamochromatosis). The test is also useful for patients with high cholesterol levels but without a detectable FH mutation.
CVD multigene test* Includes selected gene variants implicated in • Lipid / cholesterol metabolism • Folate / homocysteine metabolism • Coagulation / blood clotting • Iron homeostasis	Moderately raised plasma cholesterol levels (<7.5 mmol/l) and/or elevated homocysteine or iron levels, or family history of CVD or thrombosis. This nutrigenetic test combines diet, lifestyle and genetic risk to provide a personalised program to reduce CVD risk.

*A medical and dietary assessment is performed and health guidelines provided based on family history, personal medical conditions, environmental risk factors, biomarkers and the genetic profile.

The CVD test concept developed in South Africa and patented by the Medical Research Council in 2001, provides a model to also address the lifestyle link in many other multi-factorial medical conditions of major clinical importance worldwide. It represents the prototype for future development of novel pathology supported genetic tests (Figure 1) as part of the Genome Research Innovation Initiative launched in April 2008 by the Department of Pathology, University of Stellenbosch (Schneider 2009). Identification of genetic causes of disease and factors that may contribute to disease severity or future risk, allows the formulation of individualised treatment plans tailored to the needs of the individual.

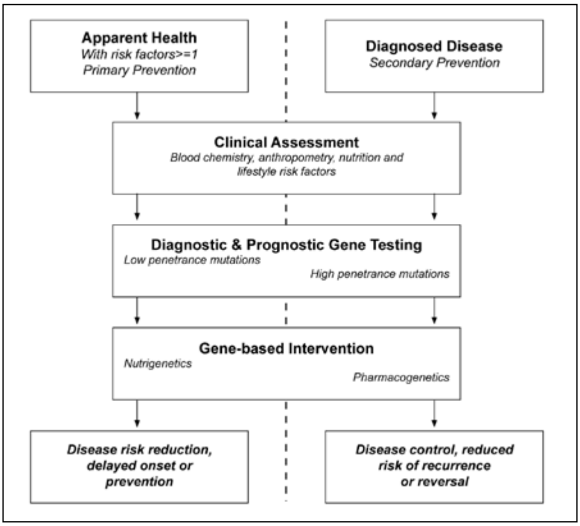

Figure 1. Risk management of cardiovascular disease as a model system for multi-factorial conditions with a genetic component. This genomic approach includes evaluation of the current health status of the individual, documentation of the family history, and pathology supported gene-based intervention based on the overall risk profile. Copyright Gknowmix (Pty) Ltd. © 2007-present.

Since the Cardiovascular genescreen includes the analysis of both low- and high-penetrance mutations where appropriate, more than one genetic risk category is addressed. The genetic test result is not evaluated in isolation, but is correlated with biochemical parameters and clinical features relevant to CVD risk. Genetic test results are therefore not evaluated primarily to define risk (Kotze et al. 2004), but rather to use this information together with data generated from a medical and lifestyle assessment to develop a risk reduction program in relation to the gene variations identified and relevant blood biochemistry expression levels.

This clinically integrative genetic testing approach can also be applied as part of Wellness Programs offered by medical schemes and clinicians involved in workplace health initiatives. The aim is to exclude the possibility:

1. That causative genetic factors are missed (which may benefit other family members who could then be screened for the same mutation following genetic counselling), and

2. That the effect of modifier genes (low-penetrance) acting in combination with the faulty gene (high-penetrance) are not taken into account. A catalogue of clinically-useful pathology supported genetic assays is built as part of an educational program to underpin the growing number of personalized medicine applications.

The purpose of the Gknowmix Online System

The Gknowmix online system was designed with a clear vision to 'create healthier individuals' through the application of genetic knowledge generated by the participating research and service delivery teams including scientists, genetic counsellors and clinicians. This combined knowledge is packaged in the form of genetic tests, or a package of relevant genetic and pathological tests, grouped according to the diagnosis and/or treatment of a specific medical condition such as CVD, Alzheimer's disease, pregnancy complications, some forms of cancer, etc (Kotze et al. 2005a-d, 2006).

As a first step, scientists working in close collaboration with clinicians are invited to incorporate their genetic research discoveries into the Gknowmix system. This research translation phase involves designing specific templates (questionnaires) incorporating family history, pathology, environmental factors (e.g. use of medication, dietary intake and exercise levels) and genetic testing. The integration of this data into an automated report format is performed by the Gknowmix expert system (logic engine) for final interpretation by a member of the research team (medical scientist) before release back to the referring clinician.

Scientists and clinicians can thus continually improve and grow the system while using the Gknowmix system tools in parallel for research and genetic testing service delivery. These tools have been built around sound business logic. IT in the form of a website makes a larger client base easier to manage, and thus creates the opportunity to reach a substantial number of patients.

Service Delivery Linked to Research Initiatives

When conducting research, medical scientists have certain resources at their disposal. These resources can be physical (e.g. human resources, inventory used for tests or pricing), or non-physical (e.g. information and time). The Gknowmix system tools have been designed to provide participating scientists with an overview of these assets available to them; an easy way to manage the assets; and a way to ensure that 'outputs' are supported by sufficient 'inputs'. Thus the system in fact could also be described as an online business platform, or a website that incorporates resource planning for the scientist's benefit. Because research projects can be better managed through use of the Gknowmix tools, application of the same system for research and service delivery would ultimately benefit the patient.

Development of the Gknowmix system included both a 'phased build' and 'phased implementation' plan. The overall objective is to reduce system complexity in the mind of its users by making the system accessible and easy to use. The immediate aims are to:

1. Enlarge the 'client' base so that more patients can be reached (where clients refer to both clinicians and scientists – the users of the system)
2. Provide 'business' training for students who are using the system (Gknowmix works in partnership with several academic institutions)
3. To see a national growth in medical research and collaboration between clinicians and scientists through a high level of service delivery accomplished through the use of the Gknowmix online system

Because research projects can be better managed through use of the Gknowmix online website tool, this benefits the scientist, and ultimately, the patient. The system enables the scientist to provide a service to the clinician and both sets of users can easily manage and exchange data and information in 'real-time' as is needed.

Benefit to Medical scientists

Scientists who use the Gknowmix system focus on making genetic testing (supported by pathology) available to the public via an educated clinician network. As they may want to maintain the role of a scientist (rather than a full-time entrepreneur) a 'point of contact' for clients was created through establishment of a virtual Genetic Care Centre (www.genecare.biz).

Efficacy of the business process is based on the following principles:

- The more business transactions that can be automated through the website, the more service transactions the business will be able to complete. Thus it fully supports business growth.

- While the website is easily accessible to the public, it also provides a single point on which data can be accessed and managed by the business owner (scientist). It allows a business to operate more smoothly.
- Business processes can be pre-planned and designed and taken from 'best practice' principles. This is how the Gknowmix system has been planned and how additional components of the system will be included.
- Standardising business processes; building it into a system, and then documenting them in a way that can easily be understood by users, makes the product more 'sellable' and accessible to clients and prospective clients.
- Being able to take a client through from first contact to payment, and managing this data flow is facilitated by building it all into one web-based system, thus allowing the organisation to provide a better service.
- The database stores client, accounting and inventory information that leads to better management of information; easy access; personalised service; increased customer satisfaction and thus increased revenue.
- Standardisation and integration result in better sharing of information within the business and between the business and the client, reducing errors that manual processes often produce because of a lack of system controls and segregation of duties built into the online web based system

The Gknowmix website was planned so that it would be a complete service delivery engine and database tool built around sound business logic so that a scientist can easily provide a service to an end-user. The aim in building the Gknowmix online system should result in a full collaborative platform on which all business functions are included and supported. To fulfil the vision, the system needs to be used by other scientist to develop new products and services aimed at reducing the burden of complex medical conditions with a genetic component.

Conclusion

Transformation of the current curative medical model to a more cost-effective, preventive healthcare model is hampered by the lack of integration between clinical risk and genetic risk information. Gknowmix.com can fill this knowledge gap with its multi-disciplinary professional web interfacing model that seamlessly integrates the different professional activities required for genetic testing service delivery.

The following workflow process utilizing the Gknowmix software system translates into comprehensive patient reports for clinical decision-making:

1. Clinicians: Patient consultation, clinical assessment and referral
2. Genetic counsellors: Genetic risk assessment and counselling in a family context
3. Laboratories: Pathology, molecular genetic testing and analysis
4. Medical scientists: Data interpretation and authorization of reports

Knowledge input at different interactive web interfaces contributes to a genetic database providing a valuable resource for future research. Gknowmix represents the cutting edge synergies of biology (genomics) and engineering (ICT), an intersection that is changing the face of medicine globally from a curative discipline to one based on risk identification, prevention and targeted treatment. The Gknowmix vision is to make the system and its tools available for the use of medical scientists and clinicians as the gateway to genomic healthcare.

Acknowledgements

Code Green (Pty) Ltd. is acknowledged for development of the unique Gknowmix logic engine in a way that enables scientists to incorporate a growing number of integrative healthcare applications based on elucidation of gene function.

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A Systems Biology Approach to Translational Medicine and Wellness in Venezuela

Rafael Rangel-Aldao

Systems biology is on the verge of producing radical changes in clinical medicine to allow the prediction and prevention of major causes of morbidity world-wide, in particular, common and costly chronic ailments such as cardiovascular disease, cancer, obesity and type 2 diabetes. These diseases are connected by networks of biological information regulated by overlapping hubs of genes and/or regulatory proteins, especially those pertaining to both the stress and the chronic inflammation response. Diseases may not then be considered as separate entities, but the consequence of disequilibrium of complex networks spanning the individual's physiology in response to particular environments. The emphasis is now on how to collect, from normal subjects, enough network information of predictive value to preserve a person´s wellness as well as to avoid or retard the advent of disease. The work presented here consists of an experimental attempt to field-test such a rationale with a multidisciplinary approach in the form of stacked networks of scientists, health care professionals, volunteers and their employers.

Introduction

Systems biology is on the verge of changing the current paradigm of health care by substituting reactive and determinist medicine into a branch of information science and technology with predictive and preventative power.

New tools derived from a combination of information and communications technologies with sophisticated mathematical techniques allow the translation of cutting-edge knowledge from biomedical sciences into a new type of medicine in which patients can be seen to by empowered physicians with the help of multidisciplinary teams of scientists. In this fashion it is now possible to interrogate and obtain key information from biological networks of information pertaining to each individual, and, therefore, to predict risk and prevent or retard the advent of clinical manifestations of major and common diseases (Rangel-Aldao, 2010).

This type of approach combined with genomics and proteomics is also a very important factor in the emergence of personalized medicine (Burrill, 2010). The applications of genomics are primarily based on the use of genome-wide association studies with disease (GWAS), that is, the study of single nucleotide polymorphisms (SNPs) linked to major illnesses such as cardiovascular disease, cancer, obesity and diabetes, together with clinical and metabolic indices of risk (Kathiresan et al, 2008).

The predictive value of such studies, however, is less than optimal to say the least, as stated by Manolio (2010): 'Despite their value in locating the vicinity of genomic variants that may be causing disease, few of the SNPs identified in genome wide association studies have clear functional implications that are relevant to mechanisms of disease (Hindorff et al, 2009). Narrowing an implicated locus to a single variant that directly causes susceptibility to disease by disrupting the expression or function of a protein has proved elusive to date. This will be a key step in improving our understanding of the mechanisms of disease and in designing effective strategies for risk assessment and treatment.'

An equally important contributor to this new paradigm is the advent of digital medicine, and consumer oriented digital health, by which the patient takes responsibility of his/her own health care, empowered by patient controlled Electronic Medical Records (EMRs) and telemedicine that allows real time connectivity with either his/her physician or the hospital as needed (Burrill, 2010b).

In Venezuela we have bundled such advances into a technology package and a start-up company, Summum.Net, that evolved from a previous but limited attempt called Genotron (Rangel-Aldao, 2010). The difference is in the lower emphasis of the former on genomics to predict risk for common diseases such as those listed above.

Three hypotheses set forth before for Genotron (Rangel-Aldao, 2010) are still valid for Summum.Net:

1. Biological information is essentially organized at the molecular level into small-world and scale-free complex networks where few nodes (genes & proteins) become hubs dominating the entire network (Barabási A-L, Oltvai ZN, 2004)
2. Such knowledge, emerging from systems biology, could be translated in most countries into this new type of molecular medicine, predictive, preventative, personalized and participatory (Hood, 2007)
3. 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.

These three hypotheses are used as a theoretical background to launch a unique synthesis of the four emerging technologies referred above, that is, personalized medicine; consumer oriented digital health care, preventative medicine and worksite wellness programs. To make this happen, we use the power of virtual integration in health care by multidisciplinary and interacting networks (Rangel-Aldao, 2005) as shown below.

The Summum.Net Synthesis

Summum.Net is a network of networks consisting of a central hub of scientists and engineers to build a system of EMRs, electronic portals (EP), management and finance, linked to key nodes of distributed networks of practicing physicians (internal medicine and occupational medicine), nurses, molecular biologists, mathematicians, physicists (complex systems), computer scientists and engineers, psychologists, psychiatrists, nutritionists, and physical trainers, organized as depicted in Figure 1.

With this sort of collaborative arrangement, Summum.Net applies the Healthium Plan in an attempt to merge four emerging technologies and markets such as personalized, digital, and preventive medicine, with wellness, as depicted in (Figure 2).

The Healthium Plan

The main objective of Summum.Net is to use a systems approach to health care and provide employers with a digital system of physical health for each

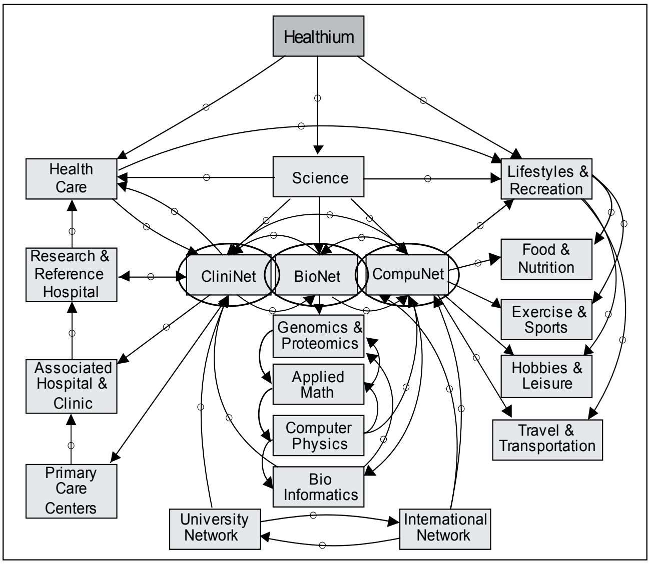

Figure 1. The Summum.Net Web and the Healthium Plan. Science bridges two seemingly unrelated fields such as Health Care and Lifestyles and Recreation, by means of three specialized networks of physicians and nutritionists (CliniNet), molecular biologists, bioinformatics and genomic experts (BioNet), and mathematicians, physicists, and computer engineers (CompuNet). All networks are connected to hubs of local universities and international centers of excellence abroad (Rangel-Aldao, 2010). The Healthium Plan is a seamless connection of corporate customers of Summum.Net with providers of both health care and personal recreation as depicted in the illustration.

employee to improve labor productivity and wellness for each participating individual. The sequence of events follows three phases illustrated in (Figure 3).

The Healthium Plan provides Summum.Net with a data base containing over 80 discrete variables that span from demographic, personal and familial background data, lifestyle habits and consumer preferences, biometric and metabolic indices, to physical findings, diagnostic recommendations, medicines, exercise, and so on. The database is subjected to statistical analyses with many types of data mining algorithms including decision trees, vectorial support machines (VSM) and neural networks to discover novel indicators of risk to cardiovascular disease and metabolic syndrome, among other common illnesses.

Figure 2. Emerging technologies and markets merge at Summum.Net. The boxes corresponding to each quadrant represent enablers of Personalized Medicine, such as a private doctor and a molecular systems approach to monitor the hubs of bio-information networks for each individual; Digital Medicine, comprises the use of web-based wireless devices to monitor vital signs and EKG, among other parameters of health, as well as a complex systems approach to monitor populations; Preventative Medicine, consist in the determination of risk vectors to major and common diseases, early intervention to prevent or retard the appearance of such illnesses. Mezzanine Medicine pertains to physician empowerment with genomics and proteomics. Wellness is attained by providing personalized information based on individual EHRs, as well as small financial incentives and rewards for a good health status.

To illustrate the power of data mining, Figure 4 depicts the results of such an exercise where we can observe how some of these variables organize by themselves to show a hierarchy of importance on cardiovascular risk, for example.

(Figure 4) clearly shows that within this limited sample of 1,300 homes, the number one factor to take into account to assess cardiovascular risk is the level of education of each person, being the probabilities of level three (university degree), lower than those of two and one, which correspond to secondary and grammar school, respectively. The second factor in the hierarchy, surprisingly enough, was the ownership of a car as well as the existence of previous medication. Next levels were, predictably, stress and age, two well known factors of cardiovascular risk.

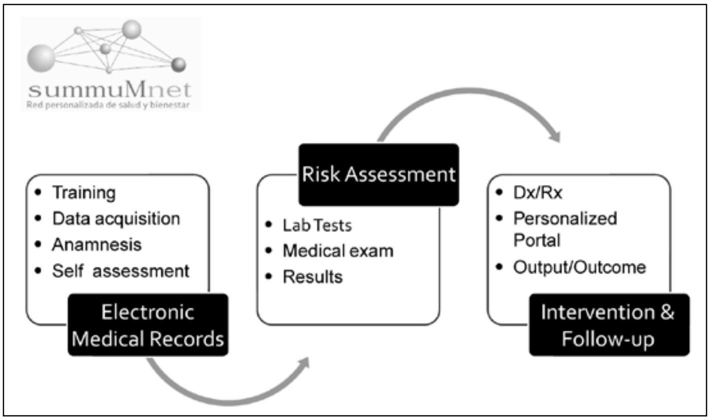

Figure 3. Three stages of the Healthium Plan. Electronic Medical Records are accessed at (http://www.summumnet.com) and filled by each participating individual. Risk Assessment is then measured by a combination of questionnaires, clinical lab tests and physical examination on site by a qualified physician (private doctor). Intervention and Follow-up is performed and monitored through a secured Personalized Portal that displays the EMR, doctor's recommendations, and a host of services to help each participant to stay healthy. Privacy is preserved with the highest standards of encriptation and anonimization of EMRs that can only be accessed by the participant and his/her private physician.

Car ownership as a protection factor to cardiovascular disease may not be a total surprise if one takes into account the poor quality of public transportation everywhere in Venezuela, and it may also be the case in other countries with similar conditions. The finding, however, highlights the use of data mining as a powerful tool to find other non obvious factors of risk to common diseases, such as being a housewife, for instance, or not owning a home, as our preliminary data seems to indicate with a larger set of variables.

The following stage of this ongoing project is to scale it up by using high throughput wireless equipment to standardize and measure as much over 100 variables spanning physical examination, clinical laboratory, genomic analyses of SNPs of key genes involved in the unfolded protein response and chronic inflammation as well as with type 2 diabetes and obesity (Rangel-Aldao, 2010).

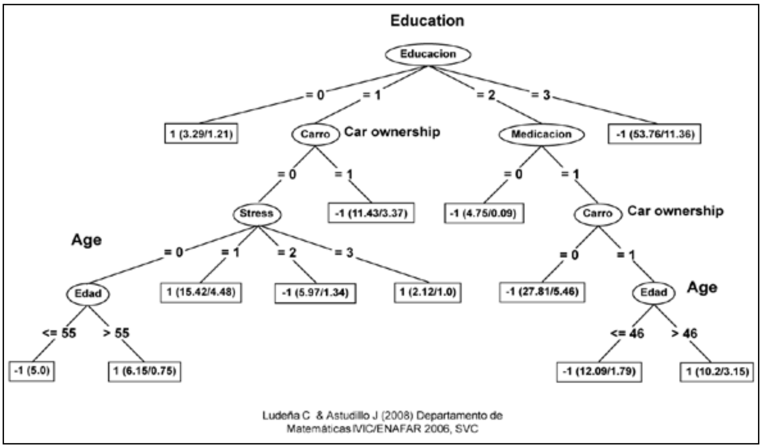

Figure 4. Classification of cardiovascular risk via decision trees in WEKA. The example illustrates the use of machine learning algorithms for data mining tasks using the J48 classifier in WEKA (http://www.cs.waikato.ac.nz/ml/weka/). The data was obtained from a nation-wide study performed by the Venezuelan Society of Cardiology (2006), of 1,300 homes of people 18 years and older. The numbers shaded in boxes correspond to probability. Zero and one refer to the absence and presence of the indicated attribute (i.e., stress, car ownership).

Conclusions

This attempt of many years to translate systems biology into predictive and preventative medicine in Venezuela (Rangel-Aldao, 2005, Rangel-Aldao, 2007; Rangel-Aldao, 2010) has finally become a practical reality. Through Summum.Net, in close collaboration with Simon Bolivar university, we have established a hub to link multi disciplinary networks made of scientists and technologists from public universities and private companies spanning several branches of engineering, medicine, molecular biology, genomics, mathematics, and emergent computing for data mining. Thus, it is possible to practice this sort of integrated and advanced technologies to improve the health care system of developing countries such as Venezuela.

Acknowledgements

The author is indebted to Drs. C. Ludeña and J. Astudillo, from the Department of Mathematics, Venezuelan Institute of Scientific Research (IVIC) for the data mining study shown on Figure 4. Equally important was the editorial review and technical contributions to the Electronic Medical Records of our production engineer, C. Cortejoso from Summum. Net. We also acknowledge Dr. R. López Nouel and the Venezuelan Society of Cardiology, for supplying us the raw data of the nation-wide study of cardiovascular risk, ENAFAR 2006.

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Biodiversity Prospecting for Drug Lead Discovery in Latin America

Barbara N. Timmermann

Summary

An International Cooperative Biodiversity Groups (ICBG) Program was established at the University of Arizona in 1993 for research into drug lead discovery from plants, biodiversity conservation and economic development in Latin America. While biodiversity from arid lands is well known to produce a vast array of natural products as defensive agents and poisons, they have received much less attention than plants from the tropical rainforests as potential sources of drug leads for human health. This project funded by the U.S. government, has been undertaken in cooperation with universities and research institutions from the U.S.A., Argentina, Chile and Mexico, and U.S. pharmaceutical and agrochemical corporations. The ICBG program is unique in its emphasis on the United Nations Convention on Biological Diversity regarding the implementation of policies on conservation of natural resources, intellectual property rights and other issues of concern to host countries.

Introduction

Medicines from plants with biological/pharmacological activity have a long history of use in both traditional and modern societies as phytomedicines, herbal remedies, purified compounds approved by the Food and Drug

Administration (FDA) and as starting materials for further chemistry or biocatalysis modifications. Drug lead discovery from plants still provides important new drug leads against diverse diseases such as cancer, malaria, HIV/AIDS and tuberculosis. However, drug discovery from plants faces many challenges, including legal and logistical difficulties involved in the collection of plant materials, the lengthy and costly process of bioassay-guided fractionation, isolation and chemical characterization and the elimination or reduction of natural product research programs at pharmaceutical corporations and U.S. federal agencies.

Beginning in 1993, the International Cooperative Biodiversity Groups (ICBG), a program administered by the Fogarty International Center (FIC), National Institutes of Health (NIH), and supported through funds through NIH, National Science Foundation (NSF) and U.S. Department of Agriculture (USDA) Foreign Agricultural Service (FAS), started operation in an effort to integrate the following goals: improvement of human health through drug discovery, incentives for conservation of biodiversity, and development of new models of sustainable economic activity that focus on the environment, health, equity and democracy. The implementation of this program is based on the belief that the discovery and development of pharmaceutical and other useful agents from the world's biodiversity can, under appropriate circumstances, promote scientific capacity development and economic incentives to conserve the biological resources from which these products are derived. The drug discovery effort is focused on diverse target organisms, comprising five (Eubacteria, Protoctista, Plantae, Fungi, Animalia) of the six kingdoms of overall biodiversity.

The ICBG entitled 'Bioactive Agents from Dryland Biodiversity of Latin America' serves as a model for the implementation of the ICBG principles, which are, ultimately, the principles of the United Nations Convention of Biological Diversity (UNCBD). In the two phases of operation (1993–1998 and 1998–2005), and until the author moved to Kansas from Arizona, this ICBG consortium consisted of a US-based academic institution (University of Arizona), four Latin American academic and research institutions (Pontificia Universidad Catolica de Chile, Santiago, Chile; Instituto de Recursos Biologicos, Buenos Aires, Universidad Nacional de la Patagonia, and the Centro Nacional Patagonico, Chubut, Argentina; and Universidad Nacional Autonoma de Mexico), one US research institution (Institute of Tuberculosis Research, Chicago) and two US industrial partners (Wyeth

Research-Pearl River, New York and Fort Dodge Animal Health-New Jersey). Based on this model, bioprospecting research continues at KU with new host country collaborations (*e.g.*, Panama) under new institutional agreements.

This international project seeked to discover and develop pharmaceutical leads and crop-protection agents from plants of arid and semi-arid ecosystems in Argentina, Chile, and Mexico. In addition to scientific study, the work promoted economic growth in areas where the plants were collected, involved local populations wherever possible, collected indigenous knowledge about the plants and their uses, and worked to conserve biological resources through educational programs.

This project has involved plant collection, extract and fraction preparation, screening of extracts and fractions in cytotoxicity and mechanism-based in vitro bioassays, de-replication of active plant species, activity-guided fractionation, compound isolation and structure elucidation, in vivo testing in animal models, lead optimization, and compound development. Although extensive data have been collected through the course of this project, this paper describes the different projects within the program in regard to plant procurement, drug lead discovery, conservation activities as well as intellectual property rights and issues of concern to host countries.

Plant Procurement

Many xerophytic plants are known for their medicinal properties and for the complex arrays of natural products they manufacture as apparent adaptations to extreme conditions of heat, desiccation, ultraviolet radiation, and herbivory to which they are exposed. Arid-adapted plants are noteworthy by providing host plant defenses against infectious disease, parasitism or predation.

This ICBG program focused on plants from different regions in Latin America and allowed for the systematic screening of medicinal, endemic and local plants with a battery of high throughput biological assays. The feasibility of a plant-screening program depends on effective procurement strategies using a combination of random, biorational and ethnobotanical strategies.

In order to incorporate national priorities into the site selection process, regions of high interest for conservation as well as community development were considered as recommended by governmental and non-governmental conservation organizations in each host country. Plants collections were undertaken in diverse ecosystems such as the cold deserts and steppes of Patagonia and Tierra del Fuego, as well as the phytogeographical provinces of the Monte and the Chaco in Argentina; the hyper-arid desert of Atacama and the semi-arid and arid central Chile, and the drylands of central and western Mexico.

This program was designed so that plant collections, inventories, and other activities were in agreement with the appropriate domestic and international laws, such as laws on endangered species (CITES) and plant conservation. When working in the natural areas of origin of the plants, permission was always sought at the national and local levels. In some cases, agreements were made with local non-governmental organizations and provincial governments in the source countries.

When available, local collaborators in the collection areas were contacted and interviewed about plant remedies from the local flora. This knowledge was gathered primarily to help insure preservation of this cultural knowledge, to increase the chance of drug discovery, to develop local phytomedicines and to maximize the potential of rewarding the local community with financial benefits.

Once a plant species was located in the wild, a necessary amount of above-ground biomass was collected to yield approximately one kg of dry weight of material to generate organic extracts according to established protocols. To date, more than 10,000 extracts were formatted into microtiter plates and tested for biological activity in a wide variety of sensitive, selective assay systems in a variety of therapeutic areas. About 45 different screens have been employed for the initial assays and for follow up studies. In order to maximize efficiency and avoid potential conflicts of interests, a wide assortment of mechanism-based, whole organism and enzyme-induction assays were employed in the primary screening program to detect lead extracts with interesting mechanistic properties. All plant samples were subjected to a battery of biomedical bioassays using several automated, high throughput enzyme assays developed and performed at Wyeth (Pearl River, New York) and the Institute for Tuberculosis Research (Chicago) while the agrichemical and veterinary tests were performed at Fort Dodge Animal Health (Monmouth Junction, New Jersey). Therapeutic areas of potential target applications in human health included oncology, anti-infective, central nervous system, metabolic and inflammatory disease and women's health. An extensive battery of organisms resistant to a wide variety of clinically used antimicrobial agents were employed for secondary testing of active leads.

Drug Lead Discovery

When biological activity was detected and confirmed for a sample in at least one screen it was considered a positive lead. Bulk plant collections in the order of one-to-three kilograms of dry biomass were obtained for these positive samples or hits following the initial screens. Active extracts were evaluated in a panel of secondary screens and by chemical de-replication for prioritization. Bioassay-guided fractionation of active extracts was conducted for isolation and identification of the active compound(s). Chemical novelty, activity in secondary functional assays, and in vivo results were used in the prioritization of active compounds. New active lead molecules were selected for structural modification to generate new analogs with enhanced activity.

Structure elucidation relied largely on NMR and two-dimensional NMR spectroscopy, both to establish the basic skeleton of the compounds and to determine stereochemical relationships. Proton and carbon assignments were prepared by COSY, HMQC/HETCOR, HMBC/COLOC and NOE spectral data. In addition to NMR spectroscopy, we routinely characterized isolated compounds by IR, UV, high resolution MS, LC-MS/MS, GC/MS, specific optical rotation and melting points. Capabilities for x-ray crystallography were also available.

Although the largest part of our drug discovery research remains confidential, we have been able to publish chemistry results in peer reviewed journals following the filing of a provisional patent application. To date, about 400 compounds were isolated and elucidated of which 50 are novel compounds (Waechter et al., 1999 a, b, c, 2001 a,b; Flagg et al., 2000; Caldwell et al., 2000; Mata et al., 2001, 2002, 2003; Gutierrez-Lugo et al., 2002; Rojas et al., 2003; Woldemichael et al., 2003 a, b, c, d; Khera et al., 2003; Samadi et al., 2009). The chemical classes found include simple aromatics, benzopyrans, benzofurans, unusual flavonoids, mono-, sesqui-, di- and triterpenoids, steroidal lactones, monomeric, di-, and trimeric phenylpropanoids and alkaloids.

Information and Dissemination

The goal of the information management and dissemination component has been to support the research, conservation, and economic growth efforts of the overall project by building information handling capabilities at all project sites and by promoting the open exchange of information between the cooperating institutions. Based on a survey of all project participants in each country at the beginning of the project, specific objectives were identified for follow-up. Among the various accomplishments we were able to develop general project-related communications products, build a plant database catalog integrated with bibliographic and geographic information systems (GIS) functions and provide technology transfer and training in the use of these information systems. Throughout the course of the project, these objectives have remained largely the same, although specific activities changed and evolved according to newly identified needs and interests.

Conservation and Infrastructure Building

One of the project's central goals was to address and promote biodiversity conservation and sustainable economic activity, including development of strategies for minimizing negative environmental impacts while ensuring that equitable economic and social benefits from discoveries accrue to the country, community, and organization which facilitated the discovery of the natural product. Several workshops were held to insure that biodiversity, intellectual property rights, and cultural issues are considered in the process of prospecting for plant resources.

Conservation and development goals were closely linked to this ICBG's academic research process. The plants collected for drug lead discovery purposes formed only a part of the information gathering process. Research to support biodiversity management was integrated into independent research projects such as the study of adaptations of native plants to the local environment; facilitating plant regeneration following harvesting for medicinal purposes; as well as growth dynamics, interactions with pollinators, defensive mechanisms against predation, and other relevant fields.

A considerable effort in this ICBG was directed toward infrastructure-building and professional training in the source countries to develop long-term collaborative and sustainable relationships between the institutions involved. Benefits associated in this project have been apparent from the start as evidenced by the support received by the affiliated academic institutions in the host countries. It is recognized that the advancement on basic knowledge on plant biodiversity and conservation was important to the academic programs of all institutions. Certain infrastructure improvements have been added such as laboratory and conservation equipment, vehicles, germplasm culture facilities and herbarium facilities. University students (US and foreign) have been trained and were being given the opportunity to use the equipment and data for their academic theses and dissertations.

Benefit Sharing and Community Development

The successful collaboration of the members of this ICBG required detailed agreements among the various participants, which defined work and funding commitments, ownership of materials, licensing rights and distribution of future financial benefits, if any. This design of the agreements resembled a wheel in which the University of Arizona served as the hub of the wheel and each of the collaborators as a spoke (Rosenthal, 1997). Seven agreements had to be negotiated individually. The challenge of this construction was the necessity to assure that all agreements were consistent with the others. The advantage of the separate agreements was our ability to address specific concerns on an individual collaborator basis.

Each two-way agreement defined the scope of work obligations of the University of Arizona and of the collaborator, responsibility for permits and for obtaining informed consent, the collection and preservation of data, ownership of inventions, confidentiality, funding support, bioassay screening, reports, responsibility to establish a sustainable agricultural source of the bioactive plant in the region of its collection, and collection and distribution of royalties to the participating parties.

Royalties, should there be any, will be divided into a 'collector's share', an 'inventor's share' and a 'conservation share'. The employing institutions of all named inventors of a patent will equally divide the 'inventors share' (45% of all royalties). Further distribution by the institutions to the inventors will be dictated by existing policies. Since collectors are not generally recognized as inventors, the collector will receive a separate 'collector's share' (5%) and the remaining (the largest) share (50%) will be distributed to a conservation fund in the area of the collection of the country of collection.

It is important to realize that the probability that this or any other ICGB project will discover and develop a commercially viable drug is quite small. For example, it is estimated that it may require the evaluation of 50,000–100,000 compounds in order to obtain a single marketable drug (Kuhlmann, 1997). Not all leads will produce a drug; nearly all (49 or 50) of the compounds that show promise at an early stage in the development process will fail when evaluated in a more advanced animal model. Therefore, the real benefits from the ICBG were in the collaborative interactions established among the participating countries, the databases developed as a result of the project, the technology transfer and the training of students and faculty through active exchange programs.

An important objective of this ICBG program was to promote local responsibility for the conservation of biological diversity. In particular, we were interested in deriving products from ecologically healthy, diverse habitats that would enhance the well being of the local people, as well as benefiting humanity generally. If an industrialized product is developed from plant material, the community from which the plant sample originated will have priority in producing raw material from in situ populations, if management allows a sustainable production. Cultivation of commercial crops in the priority community will be necessary if the natural population cannot sustainably produce sufficient material, as is very likely. Hence, the local community will benefit economically by additional jobs and tax revenue as well as by conserving habitat.

This ICBG was actively involved in community work at the request of source country schools, local communities, agricultural extension stations, and non-governmental organizations. Regular training workshops were provided on conservation of native plants to elementary and high school teachers and students as well as farmers and medicinal plant collectors and processors.

Many local communities got involved in the use of, and in the production of herbal remedies. The Mexican and Chilean Secretariats of Health, for example, were able to start the process of enforcing national regulations requiring the registry of these products. Such registration included a monographic study of the botany, ethnobotany, chemistry, pharmacology and toxicology of each plant ingredient present in the plants mostly used by the general public.

Environmental trust funds have been established in order to administer any royalty that could be generated by products derived from this project. In addition, this group collaborated with advisors of the Argentinean, Chilean and Mexican Senate's commissions that have the responsibility of drafting legislation on access and benefit sharing of biological resources.

Conclusions

This summary used one of the ICBG programs to illustrate a particular framework developed for research into drug lead discovery from natural products derived from medicinal plants of mostly xeric environments, biodiversity cataloging and conservation as well as economic development. As such, this ICBG has been specifically designed at the time for the existing scientific, technological, cultural, biogeographical, legal and technological situations in Argentina, Chile and Mexico.

In the long term, this project has built institutional and international relationships between the U.S. and developing countries that continued to grow beyond the life of the project and served as an effective model for others who seek to develop similar relationships.

Acknowledgement

This program was supported by the grant 5 U01 TW00316-10 from the NIH, NSF and the USDA. The author is very grateful for the excellent contributions of the collaborating scientists as well as the laboratory contributions of the numerous post-doctoral research associates, technicians as well as graduate and undergraduate students. The contents are solely the responsibility of the author and do not represent the official views of the funding agencies.

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WHERE NEXT FOR WATER?

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The Three R's of Water: Recycle, Reclaim and Restore

Margaret Catley-Carlson

Four areas are covered in this article: a quick scan on the dilemmas that arise from current management of water resources and food production on the planet. These together should provide for both well fed populations, and the protection of the environment. They do not. Humankind may have enough water to meet its needs, but not with the current and predicted usage. We then look at a list of specific areas in which bioscience and biotechnological improvements could made a difference to water management – within improved management structures. We next explore the specific area of improvements needed in the treatment of urban water, again spotlighting both the biotech improvements involved and the management implications. We end with a brief look at why the management issues increase in difficulty.

Global Water Management: What is the Issue?

While the overall amount of water on the planet is a constant, more and more lakes, rivers and groundwater are being overdrawn, overused and polluted. While less than one tenth of the global population lived in water stressed countries at the turn of the last century, between 40% and 50% of humankind will live in water stressed countries by 2050. This is frightening in terms of well being, health, enjoyment of nature, security – and above all food and nourishment.

Some quick facts:

- It takes one liter of water to make one calorie of energy.

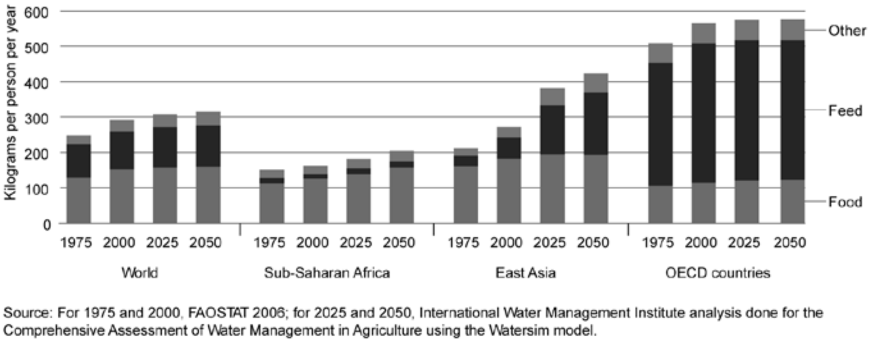

Figure 1. International Water Management Institute Analysis

- More people = more food needs = more water needs in agriculture (already accounting for 70% of the water we consume)
- More prosperity = more food protein demands = higher water needs.
- Biofuel energy – if we met 1/5 of our fuel needs with biofuels, the water consumed would equal all the water used in agriculture today.
- Populations are still growing – the global total is now past 8 billion; the maximum and fastest population growth will generally occur in the most water stressed areas.
- Agricultural water demand is sharply increasing. Municipal and industrial water use show sharp increase. Most foresee another 2.5 billion persons added before the growth stops.
- Agriculture is by far the largest contributor to water pollution: fertilizer and agricultural input runoff, being the greatest source.
- By 2025 water withdrawals supporting the planet's economic and agricultural systems will increase by 50% in the south, and 18% in industrialized countries.
- Climate change forecasts are firming up to predict real regional water shortfalls
- Recent food price doubling, tripling showed that food trade will attract speculative funds, and that protectionist responses will be swift and widespread.
- Groundwater depletion – we are headed for brick wall in many key areas: China, India, Western USA
- 70 River Basins are closing which means that no more water can be taken from them. This affects – 1.4b people who have no water left for more development if today's patterns of use continue: Yellow River, Colorado, Amu/Syr Darya, Murray-Darling, Egypt's Nile, Lerma-Chapala, Jordan, Gediz, Zayanda Rud, Indus, Cauvery, Krishna, Chao Phraya.

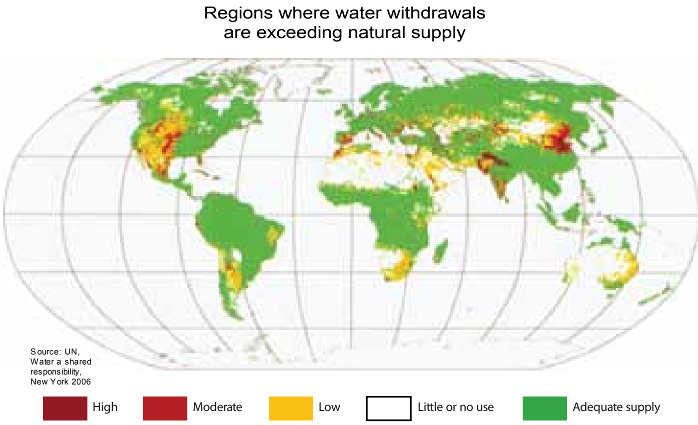

Figure 2. Regions where water withdrawals are exceeding natural supply.

Where and how do we look to bioscience?

Biotechnological advance is central to the future we need to create in water. To name but a few areas where new research will be key:

- We need to build on the success achieved in improving food production worldwide through working in intensification and improvement, rather than allowing more land to be brought under production – and more biodiversity lost
- Science must guide us so that water use in agriculture can maximize the crop per drop (but this may well be constrained by continuing constraints regarding bioengineered crops)
- Crops must be developed to withstand the stress of drought (some but not all of these will be genetically modified which will raise trade and standards issues)
- We must be able to monitor, measure and govern groundwater use. (yet in many if not most countries there is almost no regulation for groundwater extraction)
- We must develop the science and the instruments to guide watershed management from top to bottom (in most countries the process of establishing water basin analyses and strengthening the preservation and protection of source water is in its infancy)
- Good science and technology will allow us to capture the nutrients from used water, which help crop production and facilitate water recycling (there are social taboos at issue: more important, most wastewater in the south is neither captured nor treated. Issues of priority, budgeting, financing and public policy are all at play).

Changing Urban Wastewater Management Practices

The facts are startling: Most studies point to the fact that domestic wastewater is the principal cause of organic pollution (at 48%) of our water bodies. Yet, only 3% of investments in water supply and sanitation were going to sanitation and sewage treatment.

- A major factor contributing to investment delay is exorbitant cost of building or extending new systems especially in major cities. Applying traditional concepts means that miles of pipe are needed to collect carry away and process the water wastes. Significant energy is required to deliver water and to process waste (often 30–40% of municipal energy bills) – so change can bring significant energy savings.
- Wastewater irrigation is common in three out of every four cities in developing countries. Probably close to 20 million ha are irrigated with raw or diluted wastewater (10% of Asia; 2 x Africa). Often practices are not safe for the producers or consumers. This can be changed.
- With system revision it is possible to harvest energy and resources in the waste. Current techniques and designs render these less accessible through wholesale collection from highly differentiated sources and massive dilution.
- New technology creates new possibilities – most of them in use, in part, around the world. Membranes create extraordinary range of possibilities – especially with new system designs:
- Technologies that create 'cascading use' – bioscience and biotech deeply involved in creating and monitoring the system components.\
- New cities installations and refits of older systems designed around the cascading, modular system.
- Start with clean water for drinking and personal use:

    1. Cascading down to grey water which can be 'cleaned enough' for agricultural, urban, and industrial use
    2. Which in turn can be 'cleaned enough' for recycling or environmental recharge etc
    3. Sewage, either harvested for energy and/or nutrients then 'cleaned enough' for agricultural or environmental use.
    4. Filters, energy sparing devices, re-use devices, reed bed examples
    5. 'Systems designed to be as small as possible – as big as necessary': water treated to be only 'as clean as necessary' for the next use.

- To quote but one example from Asia: A recent World Bank report pointed out that Metro Manila was second to the lowest in sewer connections among major cities in Asia at less than 7%, compared to 20% for Katmandu, Nepal and 30% for Dhaka, Bangladesh. With all the risk factors that may develop with unsafe water, the implementation of the Philippine Clean Water Act of 2004 (RA 9275) is imperative – and yet compliance is low. Despite fines of up to P200,000, it is estimated that almost 70% of businesses in Metro Manila may have to be shut down if compliance with the Clean Water Act would be strictly monitored.

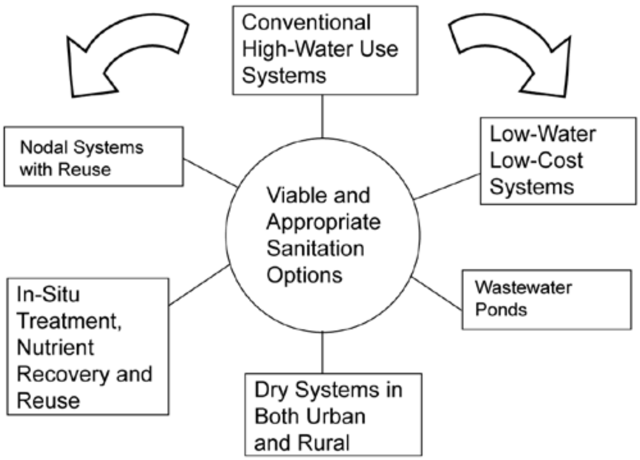

Figure 3. Creating a Portfolio of Viable Sanitation Options (International Water Association)

Why is Change of these Magnitudes so Difficult?

There are a number of important factors here:

- There is no international organization for water, as there is for health, agriculture, weather etc. New ideas must percolate via informal networks. Often the political and financial players are not aware of new possibilities created by new technologies.
- Engineers talk to engineers; city managers to elected officials etc. Some creative cross hatching is needed.
- Wastewater systems basically replicate the original systems designed for compact, water-plenty northern cities.

- We don't value water:
  - Irrigation systems – 40–60% efficiency norm in too many places
  - Municipal systems – 30% unaccounted for water
  - We leave taps running – literally and metaphorically
  - We don't pay enough for it
- We don't design it in as a scarce valuable
- More and more, solutions to difficult problems can be found only in composite actions.
  - No single idea will serve – no piece of infrastructure, no new Fund, no Programme, no piece of technology, no draconian social engineering, no dramatic price movement (though these may all play roles)
  - The difficult problems of our time – global climate variability, homelessness, the obesity epidemic, narcotics trade, rational water use, finding and using cleaner energy – all of these require changes from thousands if not millions of players
  - This creates a political problem of some considerable magnitude: leaders are expected to 'do something' in response to disasters, threats and challenges. The real answer is often that a great number of players all need to 'do something'. The trick is to find the mechanisms that will increase the chances that they will move in the right directions.

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Getting Out of the Water Tank

William Cosgrove

The report World Water Vision; prepared in 2000 described the water crisis that would arise by 2025 if those responsible continued to act as they had in the past. It analyzed possible scenarios for change and described the desirable state that could be achieved by 2025 through a combination of socio-economic changes. Ten years later, the 3rd United Nations World Water Assessment Report revealed that not only was the world not on track to meet this desirable state as described in the vision, but new factors such as climate change were making the situation worse. New technologies and improved communications make other actions to redress the situation possible. It is not those who traditionally managed water who need to act, but governments, the private sector and community action groups. With commitment by these stakeholders, informed by water managers, the world water vision can ultimately be achieved.

World Water Vision: Making Water Everybody's Business

It was ten years ago on World Water Day, at the Second World Water Forum in The Hague, that the World Water Commission for the 21st Century launched its report. The Commission was chaired by Ismail Serageldin. The World Water Vision report, which furnished the background data for the Commission report, highlighted that in the 20th century, world population had tripled, but water use for human purpose had multiplied six times. Since then the population continued to grow and water use continued to rise even faster, driven also by increasing consumption with increasing income, as part of the population managed to lift itself out of poverty (even while the numbers living in absolute poverty increased). Water pollution also increased, not just from municipal waste but perhaps more importantly from agricultural drainage and industrial pollution. Pollutants that don't settle to the bottom of lakes and rivers eventually are carried to the oceans – the final sink for our waste just as the atmosphere is for the greenhouse gases humans produce.

The Vision report described four scenarios for the future of water resources on the planet. Computer models were used to quantify the scenarios. Under the first scenario, Business as Usual, a continuation of the then current policies and trends would lead to a crisis we all can imagine. Under the second, technology, economics, private sector initiatives and globalization would drive economic growth but the poorest countries would be left behind. The values and lifestyles scenario, the third, would strive for sustainable and equitable development, focusing on research and development in the poorest countries. It would limit water and food scarcity, but not overcome them. The fourth scenario, a normative scenario, was designed to achieve the World Water Vision by 2025.

The Vision foresaw that by acting to change our practices, in 2025 we could be living in a world with a population of 7.5 billion people where everyone would have access to safe water supplies. Agriculture would produce enough food so that no one need go hungry. Reduced global consumption by industry would accompany substantially higher economic activity in the emerging and developing countries. Similar concern for freshwater and the environment would have reduced the volume of waste from human activity and led to the treatment of most solid and liquid wastes before their controlled release into the environment.

3rd Edition United Nations World Water Development Report

Ten years later I found myself Content Coordinator of the 3rd Edition of the United Nations World Water Development Report. This report was published a year ago at the 5th World Water Forum in Istanbul. It is worthwhile recalling some of its messages.

Water-related crises

The report noted that the news media were full of talk of crises – climate change, energy and food prices and troubled financial markets. These arise against a background of continuing poverty for a large part of the world. They are linked to each other in many ways, not least of which is through their links to water resources.

Prices for energy go up with demand for heat, light, power and transportation, is increasing rapidly. According to the International Energy Agency, the world will need almost 60% more energy in 2030 than in 2002, with economic growth in developing countries driving most of the increase.

In his introductory presentation Ismail Serageldin indicated potential causes for the steep food price increases we observed in the spring of 2008. These include:

- Rising demand from population increase and shifting diets
- Droughts
- Cost of agricultural inputs – which were rising with energy prices at that time
- Agricultural land and water being used for biofuel

The contribution of the global financial crisis was as yet unknown.

We have always been subject to climate variability, and still do a poor job of managing it in many places. It requires major investment to avoid losses as illustrated by impacts on GDP in Ethiopia and Tanzania. In Ethiopia a World Bank study showed that over a 12 year period up to 38% of GDP could be lost and poverty increased 25% through unmanaged climate variability.

Competition for water exists at all levels and is forecast to increase with demands for water in almost all countries. Increasing demand for water threatens the sustainability of fragile ecosystems. Population growth, increasing consumption per capita and climate change will increase stresses in regions already stressed. In 2030, 47% of world population will be living in areas of high water stress. So while water must be managed locally, the accumulation of local water crises has led to a global water crisis.

Possible consequences of ignoring the importance of water

What will happen if we continue to ignore the importance of water in resolving these crises? The possible consequences in one situation were well-described by Ban Ki-moon, UN Secretary-General, 2008:

'Ten years ago—even five years ago—few people paid much attention to the arid regions of western Sudan. Not many noticed when fighting broke out between farmers and herders, after the rains failed and water became scarce. We can change the names in this sad story. Somalia. Chad. Israel. The occupied Palestinian territories. Nigeria. Sri Lanka. Colombia. Kazakhstan' and much on my mind these days, Haiti. All are places where shortages of water contribute to poverty and insecurity.

External forces affecting water resources and uses

Alongside the natural forces affecting water resources are new human activities that have become the primary 'drivers' of the pressures affecting our planet's water systems. Our requirements for water to meet our fundamental needs and our collective pursuit of higher living standards, coupled with the need for water to sustain our planet's fragile ecosystems, make water a unique challenge. The drivers examined in WWDR3 include:

- Demographic (population growth and distribution)
- Economic (globalization, rising cost of food and energy, trade and 'virtual water')
- Social (lifestyles and consumption patterns, poverty, education, culture and values)
- Technological innovation and dissemination
- Policies laws and finance (finance being the missing link)
- Climate change

History shows a strong link between economic development and water resources development.

Abundant examples can be drawn of how water has contributed to economic development and how development has demanded increased harnessing of water. Such benefits came at a cost and in some places led to adverse environmental and social impacts.

What is surprising is why there is not more investment. Because it pays!

For example in the US, every dollar invested in water infrastructure by the USACE from the early 1930s (in response to the global recession) until the end of the century produced benefits estimated at six US dollars. WHO recently reported that each dollar spent on safe water supply and sanitation has brought benefits valued at between 3–30 dollars, depending on the technology and the region.

The Paradigm Shift

Managing water resources is essential to social and economic development, poverty reduction and equity and to achieving the Millennium Development Goals. Specialists and managers in the water domain, or 'water box' have long been aware of this. But often we have had a narrow, sectoral perspective. And we do not make the decisions on development objectives and financial resources needed to meet these broader objectives. (See Figure) Other stakeholders, in government at all levels and the private sector make these decisions, influenced by community based organizations.

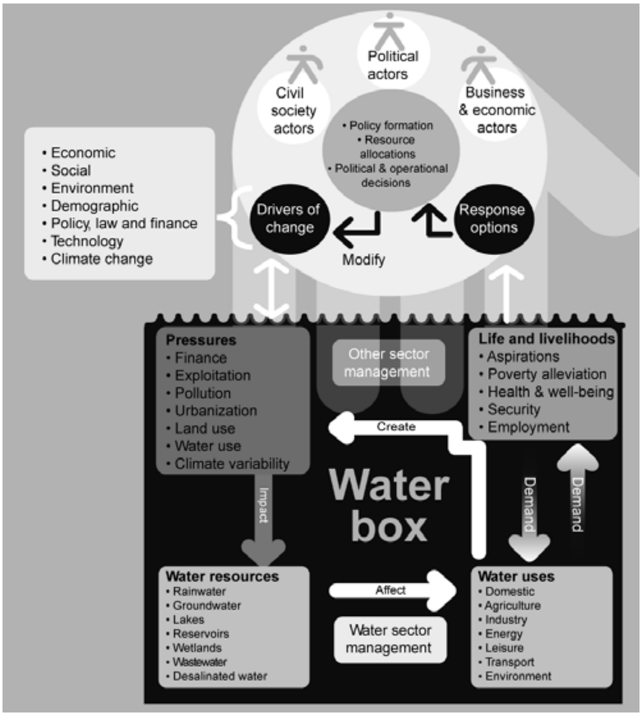

Figure 1. Getting out of the Water Box

Meeting the challenge

The report concludes saying the challenges are great, but the unsustainable management and inequitable access to water resources cannot continue – because the risks of inaction are even greater. Leaders in government, the private sector and civil society must learn to recognize water's role in achieving their objectives.

What Progress Has Been Made?

Comparing the state of water management at the time of the Vision with that of WWDR3 it would seem that little has changed in the ten years since the Vision report. Is this really the case? There has been some progress. As WWDR3 noted there has been some progress. At the Johannesburg World Summit on Sustainable Development in 2002 the world's leaders recognized the importance of IWRM. A significant percentage of countries have put in place water resource management (WRM) plans, strategies and legislation. Globally we are on track to meet the drinking water objectives of the MDGs. This reflects increased investments in that sector following the report of the Camdessus Panel in 2003. At least among water managers, there is increased knowledge of the stock and quality of groundwater in most regions of the world and how its conjunctive management with surface waters can contribute to meeting the challenges. Industry is increasingly aware of its dependence on water and implementing water conservation and pollution reduction plans. Approaches to gathering data using satellite technology and modeling have been developed and will facilitate monitoring trends even if not being precise in absolute terms. Community action is often producing better results than government. Public contribution to decision-making is taking root, facilitated by new information technologies. Some of the less wealthy countries are making progress that is better than the global average by establishing financially and politically autonomous, effective and efficient water institutions.

We are not on track globally to meet the household sanitation targets. In many countries where sanitation is provided at the household level, the collected wastes are discharged to the environment without treatment. Global data on progress in water supply and sanitation, such as it is, mask the lack of progress in many countries, especially the poorest. The MDGs do not reflect the important role that water resource management must play in meeting them, including the basic objective of poverty reduction through economic development. WRM strategies and legislation are often not translated to action through institutional, financial and cultural change. Investment in water infrastructure continues to be inadequate and single purpose in most places. Abuse and uninformed use of groundwater continues. Where there are processes for public participation, leading actors from business and government are often not fully involved. In an era when we need to know more about water resources and their uses, we are collecting less data. People knowledgeable about the impact on water resources of decisions and developments in other sectors are not at the table when these important issues are being discussed.

The Vision will not be achieved by 2025

The Vision scenarios assumed that it would take a few years to get the message out and understood, and a few more to put in place the strategies and policies to start action. Ten years later, based on the information contained in WWDR3, there is disappointing progress at national and global levels. It is clear that the World Water Vision will not be achieved by 2025.

A Rapidly Changing World Poses Threats and Offers Opportunities

In the meantime the world is changing at an accelerating pace. Climate change is now a fact.

The list of water related technology being explored could be better produced by this gathering of scientists from the north, South, East and West. Mine includes:

- Continual refinement of GIS with ability for real-time monitoring of agricultural crops and water quality and quantity
- Information technology permitting a global collective intelligence system, hopefully public, to facilitate knowledge management and decision-making
- Nanotechnology to replace current water sensors, water purification and desalination
- Biotechnology to grow food plants, biofuels and trees using saline or brackish water and to increase the yield, disease and drought resistance of crops
- Seawater-based food and biomass, including algal production
- Plant-based meat substitutes and (in vitro) cultured meat

In his talk at the Atlantic Water Summit in Washington last December, Hugh Grant, CEO of Monsanto told us that by 2050 we will be able to meet twice the current world demand for food – with no new land required and 1/3 less water. He forecast that the first drought tolerant plants will be in the field in 2012–2013. Of course, agricultural production could already be greatly increased through expanded use of current water-saving technologies in many regions.

Technological change is being accompanied by changes in cultures, society and governance. The human population has become majority urban. The tight weave of village society is being replaced by the anonymity of the city. Anonymity thrives in the workplace too. Consider how many products are assembled from pieces produced in different countries by colleagues who might never meet. Virtual connectedness is ordinary. It is accepted that pre-eminence of the West could end, while vigour and energy are transforming the Third World. Governments worldwide outsource public duties, while private firms turned to public coffers to socialize their risks. There is growing awareness that present human consumption levels amount to a massive redistribution of wealth from future generations to ours.

Globalization

One factor that seems to be common to both the challenges and solutions is the trend we call globalization.

Joseph Stiglitz, former chief economist of the World Bank in his book Making Globalization Work concludes that:

'For much of the world, globalization as it has been managed seems like a pact with the devil. A few people in the country become wealthier; GDP statistics, for what they are worth look better, but ways of life and basic values are threatened. For some parts of the world the gains are even more tenuous, the costs more palpable. Closer integration into the global economy has brought greater volatility and insecurity, and more inequality. It has even threatened fundamental values.'

He says it does not have to be like that. He suggests an approach that he considers is the only one that will actually work, is morally right and economically viable: cope with globalization and reshape it.

The Way Forward

Brian Fagan in his book Floods, Famines and Emperors looks at possible ways out for us, and concludes that there are only two: flee or innovate.

Fleeing to another planet is not much of an option. I, like Stiglitz, believe that the unacceptable conditions I have described can be changed – through innovative development and application of the same tools that were available when the World Water Vision was written: technology, economics and value changes. The rapid changes of the last decade make it more possible to do so.

The taking of responsive and responsible decisions is becoming increasingly difficult. It now requires not just knowledge of where we are and of past trends but, anticipating the uncertainties and opportunities of the future, knowing the options we have, and avoiding decisions whose impact we will later regret.

4th UN World Water Development Report

Recognizing this, the 4th edition of the World Water Development Report will address the question of managing water under conditions of uncertainty and risk. The report will be based on a review of the current state of water resources and their use and the challenges to be overcome in its management. The objective will be to define the range of risks and uncertainties which may be faced by decision makers. It will review tools available to both we who are involved directly in the development and management of water resources, and to those whose decisions determine the conditions under which water is to be managed.

UN-WWAP World Water Scenarios

Charting Our Water Future, the report of The 2030 Water Resources Group, (sometimes referred to as the McKinsey report) suggests a tool that will help make financial and economic decisions using the limited data that is available. The report points out however that low institutional capacity, policy and cultural barriers and the high number of stakeholders from whom action may be needed may make it difficult to implement technically feasible solutions. The trade-offs decision makers will have to face have implications related to everything from growth and jobs to trade and geopolitics. Scenarios provide tools that enable decision makers to take decisions with an appreciation of whether these decisions will work in all of the most likely scenarios for the future. The World Water Assessment Program has launched a project to produce these tools.

Everyone's input is essential

The vision subtitle was 'Water is Everybody's Business'. WWDR3 talked about this as 'Getting out of the water box'. We scientists and other water professionals have identified solutions to many of the problems. We need to be at the table when citizen organizations, the private sector and government at all levels are taking their decisions. Human society is going through rapid change thanks among others to exponential development of information management and communications technology. We are moving towards what can be imagined as a global brain, to which each of us contributes knowledge.

I still have a vision. I have a of a water secure world, for my children and grandchildren, and yours! And for the living species who share this planet with us. Through the innovations being discussed in Biovision Alexandria scientists are playing a role in making this vision a reality!

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Membrane technologies: Inspired By Nature at the Service of Life

Gilbert M. Rios

The Importance of Water

Religion & symbolism

'Before conceiving His Creation, God was in a cloud in the sky. Then He created His Throne above water.' (Hadith). In the Qur'an, water is the essential element of Creation; there are more than 60 mentions in the Holy Book. For Hinduism too, just a simple contact with the Ganges is sufficient to be cleared of any contamination. In fact water is a huge cultural heritage for all the religions.

Unique properties

The electronic configuration of the H_2O molecule gives it a great stability and a dipole character. It is because the ice density is lower than the liquid water density that ice floats on water. That is responsible for our climate as it is! If ice was denser than water, ocean would freeze with terrible consequences on our climate! Because water is quite difficult to vaporize, it constitutes also a good thermal regulator for climate. More, its high surface tension induces a good capillary rise which is very important as regards surface water and groundwater in spite of gravity, or for sap in the roots and stems of plants! Water is essential to all living organisms through its various other functions: it produces energy stored as ATP; enables a lot of reactions of enzymatic hydrolysis; insures all transport within the body and elimination of waste as urine….

Issues in our societies

Today water production for human consumption, irrigation... has become a crucial problem for a lot of countries all over the world. It is at the core of a huge debate on sustainable development, preservation of natural resources and well-being of population in a quickly changing world (increase of population, new ways of life, climate changes…)! Statistically, in our countries, the consumption per person is of about 5 m^3 of water per day roughly distributed as follows: 2 liters of water for drinking; 150 to 200 for the toilet, laundry, household; 1400 liter for industrial needs and 3500 liter for agricultural needs. Thus water is clearly a main factor for the daily life and the development of societies! The fundamental problem is not the quantity of water, but its distribution: only 23 countries have 2/3 of total global resources. If we consider 10 billion people on Earth in 2050, there will be 4000 m^3 of water available per person; so there is still room since water stress is around 500 m^3/year /inhabitant! Unfortunately, it is just a statistic. The total population growth mainly occurs in countries around equator and on sea-coasts… not at all in Canada or in desert! So the problem is not solved! It is a huge political and geopolitical debate which is now opened, with significant risks of 'wars for water'! (for the control of rivers, ground waters…). Illustrations are already given in the Middle-East, around the Aral basin or even in Asia (China/Tibet conflict…).

Resources and management

The amount of water on earth is finite: it is the same since the onset of the Earth in the cosmos! Overall, the amount of water on which we are living today is the same as that on which Cleopatra used to take her water for bath more 20 centuries ago! In the hydrological cycle, energy derives from the sun: the water flows continuously from evaporation, condensation and hence precipitation.

So there is a strong need to preserve surface water and ground water by limiting pollution. Looking for new resources, it appears that there are mainly four potential contributions:

- Ground water aquifers which represent about 30% of usable freshwater
- Integrated management for agriculture, avoiding waste by using more and more advanced technologies (computer-irrigation, drip...) or by selecting varieties that are more resistant to drought by changing the behavior of citizens
- Artificial rain which can be obtained by injecting AgI crystals in the clouds (this can induces 30 to 40% more rain)

- In MEDA- and MENA countries, strategies of desalination of salty water(seawater, brackish water) and wastewater recycling, with today a fast growing part played by 'membrane technologies'!

Artificial Membranes: A Life-Based revolution

As perfectly reminded by E.Sackmann

'Life in all its diversity became possible after nature had found the trick with the membrane. It enabled the separation of living entities from the lifeless and hostile environment under preservation of selective material exchange between the two worlds. It led to the evolution of cells the function of which depends on the well-controlled interplay and material exchange between compartments performing different functions. The reduction to two dimensions increased the efficiency drastically…'

One interesting example of biological membrane is the plasma membrane of animal cells which is represented here after.

This membrane is a three layered system, with a quasi-two dimensional macromolecular network (Cytoskeleton), an intermediate lipid/protein bilayer and a top-layer (Glycocalix) which is a macromolecular film formed by oligosaccharides. The two top layers insure various functions essential for life (provide energy, transmit information…) while cytoskeleton is mainly there to insure stability and mechanical resistance. It is worth noting that on the schema the two top layers are enlarged in thickness by a factor of about 300 as compared to cytoskeleton.

Artificial membranes

Artificial membranes are very simplistic industrially manufactured copies of these biological models as shown on the following schema of a recent material designed for gas or liquid separations.

Their objectives is the same as presented on the figure here after and already explained by Sackmann for biological membranes: separates the two fluids in order to isolate each from the other, while enabling very specific exchanges between them!

With these artificial membranes, 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).

Recent evolution

When the first semi-permeable materials appeared (semi-permeable cellulose acetate in the early 1960s), the possibility to separate molecular species without the use of heat was demonstrated on a theoretical level! But, from a practical point of view, this tremendous potential was strongly limited by the high cost of membranes and by the low fluxes… During the last 50 years, considerable improvements on both criteria have been done thank to new technologies, so to get today membrane with acceptable properties for the market. The table which follows shows the evolution with membranes for desalination.

Year	Element	Area (sq. Ft.)	Flow (m3/d)	Salt %	Volume Price ($)
1978	6 x 40	150	5.7	1.4	950
1989	8 x 40	300	18.9	1.0	875
1995	8 x 40	330	22.7	0.8	750
2000	8 x 40	360	24.6	0.5	645
2002	8 x 40	370	26.5	0.4	435
2006	8 x 40	400	34.0	0.2	550

The Why and How of Membrane Technology for Water and Related Issues?

Imitating nature as previously suggested is undoubtedly a great proposal to develop a new technology! Different criteria can be taken into account: energy and operating costs; life cycle assessment (LCA); health, environment, quality and market… Whatever the case membrane appears as the right solution because:

- Scarcity drives to use lower quality water sources (seawater, polluted surface water…)
- Environment regulations and energy constraints drive to produce higher quality effluents at a minimum expense

These points were among the main objectives of this track-event, organized within the framework of BioVisionAlexandria2010, with three sessions and about ten presentations from recognized experts coming from university and industry! How new nano-materials, new engineering concepts… can help to solve all these questions so important for well-being of population and sustainable developments of our societies?

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Membrane Advances for Water and Energy

Suzana Pereira Nunes

Summary

Membranes have increasing chances of application for water treatment, energy conversion and energy saving technologies. A key issue is the development of new polymeric materials such as nanocomposites. A short summary of activities under development in our group for preparation of membranes for nanofiltration, CO_2 separation and fuel cell is reported here.

Introduction

Two critical global challenges are to overcome shortages in:

1. Fuels and energy (finding new technologies for zero-emission energy conversion)
2. Water (finding strategies assure broad access to drinking water)

According to a report from the Intergovernmental Panel on Climate Change report, the global atmospheric concentration of CO_2 exceeded in 2005 (379 ppm) by far the natural range over the last 650,000 years (180–300 ppm) and is continuously increasing with a much higher growth rate. There is a growing demand for cleaner renewable energy carriers. Beside that, moved by political and economic reasons, each country aims at energy security and fuel independence. Even in the Middle East, where 66% of the oil reserves are concentrated, visionary projects aiming at advanced clean energy, alternative non-fossil fuel technology, as well as the promotion of advanced new energy saving technologies, is becoming reality. Excellent examples are the creation of futuristic science institutions such as the King Abdullah University of Science and Technology in Saudi Arabia and MASDAR in Abu Dhabi.

More than energy shortage, water availability is the crucial issue that the world is facing now. Only 2.5% of the world's water is potable and from that more than two-thirds is trapped in glaciers and icecaps. According to the UN, by 2025, 3.4 billion people will be living in countries defined as water-scarce.

An important question therefore is: how can membrane technology help to successfully prepare a better future with safe energy and water supply.

Membranes for Water Application

Membranes technology has already assumed a decisive position on water treatment and drinking water supply. The Middle East has currently the largest desalination plants to supply fresh water from sea water, using reverse osmosis.

This it the state-of-the-art of water supply in most countries in this region and is reflected also in modern scientific communities like KAUST, where water is coming from the Red Sea deep approximately 6 km from the shore and desalinated using membrane technology in a plant with capacity for 40 millions liter/day.

Membrane technology, mainly reverse osmosis, competes for desalination with thermal processes like multi-stage flash and multi-effect distillation. However the energy consumption is much higher for the thermal option, around 26 kWh/m^3, leading to a water cost of \$1 to 2.3 per m^3. The energy consumption for reverse osmosis is lower than 6.7 kWh/m^3 with a water cost below \$0.70 per m^3.

A second essential issue is the treatment of municipal and industrial waste water. In this area membranes are becoming more and more important, and membrane bioreactors are having a strong contribution as an emerging technology.

Although membrane application for water desalination and waste water treatment is already very straightforward, there are still important challenges requiring better membranes. Water supplies are suffering worldwide from growing contamination caused by human activity, including a variety of hormones, antibiotics, and endocrine disrupters. Effective decontamination would require much higher fluxes and narrow pore size distribution in the range of nano–and ultrafiltration, as well as low fouling sensitivity. The commercial membranes for water purification still mostly resemble the asymmetric porous films developed in the 1960s. A new generation of membranes is required also to support advanced medical processes and devices, which need very well defined porosity and could also profit from pore size changes with environment, for instance with change of acidity.

In a very recent development at KAUST, we succeeded to manufacture reproducible membranes with extremely high porosity and narrow pore size distribution. The membrane can be easily up-scaled in machines and the manufacture makes use of an elegant combination of block-copolymer self-assembly, polymer-metal complexation and supramolecular micelle formation in solution. The membrane surface can be seen in (Figure 1). The mechanism of pore formation was investigated in detail by advance electron microscopy methods. The isoporosity allows a much better defined separation of solutes of similar molecular size. The pores are responsive to pH, opening new perspectives of application, for instance aiming at biomedical devices.

Membranes for Energy

In the last 10 years my group has been devoted to the development of new materials for membrane application relevant for energy, particularly considering different aspects of hydrogen technology and CO_2 separation. The implementation of a society based on electricity and hydrogen technology is one of the most promising ways to achieve an emission-free future. However hydrogen is still mainly (95%) produced from natural gas. The transition to a hydrogen economy is expected to be a long term process starting with the modernization of the conventional energy plants, leading to drastic reduction of CO_2 emission, as well as the development of alternative energy conversion technologies and the increasing use of biofuels.

Membranes can help in the following way:

Modernization of conventional fossil power plants:

- Clean refineries (hydrogen production and processing)
- Zero emission coal plants (clean production of hydrogen and electricity)

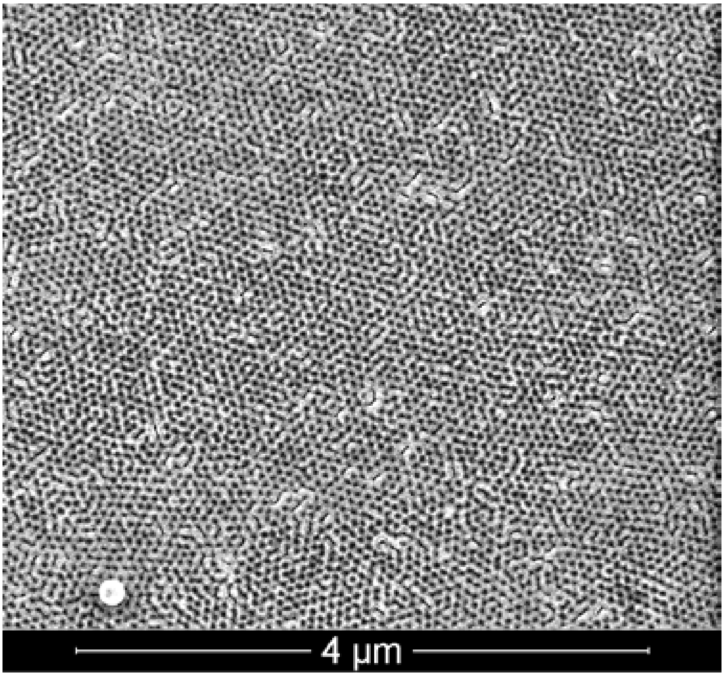

Figure 1. Isoporous membranes obtained by block copolymer self-assembly.

Renewable energy conversion:

- Fuel cells
- Wind energy (electrolysis for hydrogen production)
- Battery (for electric vehicles)
- Osmotic power

The first step toward an emission-free future is the modernization of oil refineries and other fossil fuel based power plants.

Hydrogen is currently produced in large scale from natural gas involving water-gas-shift reactor and pressure-swing adsorption as technology for purifying or enriching the hydrogen stream. As a reactant hydrogen is used in refinery in different operations and also for large scale production of ammonia and methanol. Some of the processes are performed at high temperature and would require inorganic membranes. However inorganic membranes are known for their high costs. If polymeric membranes would be available for operation at temperatures up to 250°C, they would bring a new impulse, profiting from their much easier manufacture in large scale modules. The production of hydrogen from alternative sources, using processes like artificial photosynthesis based on water splitting is attracting increasing interest and demanding membranes integrated with biomimetic catalysts.

Exploring the large coal reserves by using clean technology is another big challenge. In an integrated gasification combined cycle (IGCC) power plant, coal can be converted to hydrogen-rich synfuel for generating electricity. The hydrogen derived from the process can be used for fuel cells, with simultaneous sequestration of CO_2. Membrane technology can be applied in three different processes steps in a coal power plant:

1. Precombustion
2. Oxyfuel
3. Post combustion

While ceramic membranes is a better choice for oxyfuel, polymeric membranes could find a profitable application if better materials would be available for their manufacture. There is a demand for membranes with CO_2/N_2 selectivity above 50 and CO_2 permeance higher than 1000 gpu. Polymer membranes for CO_2 separation are worldwide under development for many years. The main problem to develop polymer membranes with preferential hydrogen transport is the high CO_2 solubility in most organic polymers. On the other hand exactly this property can be taken as advantage and be used to develop good membranes with high CO_2 selectivity over hydrogen or over nitrogen.

Our group has been developing membranes for CO_2 separation using organic-inorganic nanocomposites with functionalized fillers containing amine [8] or quaternary ammonium groups for years. This work is continuing now making use of new methods of controlled polymerization and functionalization.

Finally thinking about clean energy conversion technology, membranes are the core components of fuel cells. We have been developing new functionalized polymers, nanocomposites and blends and integrating polymeric membranes with catalysts and carbon nanotubes for years. In a recent paper acid functionalized nanotubes have been incorporated in membranes aiming not only fuel cell, but also other electrochemical applications.

Reaching optimized nanostructures for proton transport even at low humidity levels and tailoring gradients of electron conductivity, assuring high chemical stability and keeping high catalytic activities are only some of the challenges connected with membrane development for fuel cell application. The membrane is only the first step and integration with electrode, catalyst, stack design, and optimization of the balance of plant are at least as important. In collaboration with different European partners we recently coordinated the development of a 500W fuel cell stack for portable application in the frame of the project more power.

Conclusion

The main topic of investigation of my group in the last decade in Germany and now at KAUST in Saudi Arabia is the development of better polymeric materials for membranes aiming at energy and water application. New materials based on blockcopolymers, functionalized polyoxadiazole and polytriazoles as well as organic-inorganic functionalized fillers have been successfully developed in our group for nanofiltration, CO_2 separation and fuel cell. Tailoring morphology, synthesis and characterization of structures with new functional groups are now under investigation.

Acknowledgements

The membrane in Figure 1 was developed in collaboration with Klaus-Viktor Peinemann and the image was taken by Bobby Hooghan at KAUST.

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Membrane Bioreactors for Domestic Wastewater Treatment

Sami Sayadi

Summary

There are many water shortage problems currently in the world, some of which are more serious than others. All have different solutions. In several of them membrane technology can make a great contribution since membranes have the ability to produce water of exceptional purity. This study aims to assess the efficiency of membrane bioreactor technology in domestic wastewater treatment. The subject of this study is a submerged membrane bioreactor (SMBR). After the start up period the system was operated with a biomass residence time of 15 days and MLSS concentration of 4.5 g/L. Under those operating conditions the removal efficiency of soluble COD, TOC, total nitrogen and SS reach respectively 89%, 73%, 88% and 100%. After stabilization of the system a second MLSS concentration was applied (9 g/L). Thus an improvement of the removal efficiencies was recorded. The treated water is exempt of bacterial contamination. After six months of continuous work the reactor operates without membrane fouling. Results showed that the amount of total EPS didn't exceed 57.6 mg/gvs.

Introduction

Water is becoming scarce not only in arid and drought prone areas but also in regions where rainfall is abundant. In fact the Mediterranean basin (and particularly North African countries) is one of the poorest regions in the world in terms of water resources. Treated municipal wastewater is becoming one of the main alternative sources of water. However, especially in the eastern and northern Mediterranean regions, wastewaters are inefficiently treated and they are reused for irrigation or sanitary purposes. Consequently they are serving as a carrier for diseases and they are causing water pollution when discharged to water bodies.

Urban wastewater is usually treated by conventional activated sludge processes (CASP's), which involve the natural biodegradation of pollutants by heterotrophic bacteria (i.e. activated sludge) in aerated bioreactors. Activated sludge could be separated by gravitational setting (Metcarlf et al, 1991). The treatment efficiency is usually limited by the difficulties in separating suspended solids. Membrane bioreactor (MBR) is an improvement of the 100-year old CASP, where the traditional secondary clarifier is replaced by a membrane unit for the separation of treated water from the mixed solution in the bioreactor (Xing et al., 2000). Membrane bioreactor (MBR) has become a popular biological wastewater treatment technology because it offers numerous advantages over the conventional activated sludge process such as excellent effluent quality, a compact footprint, a more concentrated biomass, and a reduced sludge yield (Alain et al., 2008).

However, membrane fouling is still a major problem that hinders their more widespread and large-scale application. The membrane fouling is highly linked to the sludge attachment on the membrane surface, but it is also dependent on the properties of the biomass and the process parameters (Judd et al., 2004).

Recently, many MBR studies have identified extracellular polymer substances EPS as the most significant biological factor responsible for membrane fouling. EPSs are microbial products located on or outside cell surfaces and aggregate cells into flocs (Lee et al., 2008). EPSs include the portion bound tightly with solid surfaces and the loosely bound or soluble portion (Poxon et al, 1997). EPS have been reported not only as major sludge floc components which keep the floc together in a three-dimensional matrix, but also as key membrane foulants in MBR systems (Rosenberger and Kraume, 2005). However, many studies have shown that filamentous bacteria have significant impacts on activated sludge characteristics, such as EPS concentration, floc size, relative hydrophobicity, surface charge, floc structure and so on (Jin et al, 2004).

This research aims to study the performance of the most advanced membrane technologies working under different operating conditions.

The experienced system is a submerged membrane bioreactor (SMBR) (Figure 1). The membrane used is a microfiltration module made of chlorinated polyethylene. After the start up period the system was operated with a biomass residence time of 15 days and MLSS concentration of 4.5 g L^{-1}.

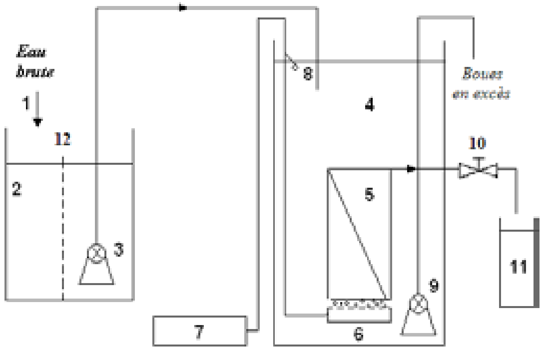

Figure 1. Schematic presentation of the reactor: 1) Raw wastewater, 2) Alimentation tank, 3) Submerged pump, 4) Aerobic Reactor, 5) Microfiltration Membrane, 6) Diffuser, 7) Compressor, 8) Level detector, 9) Withdrawal pump, 10) Automatically adjustable valve, 11) Permeate tank, 12) Grid.

Results

Influent characterization

The influent composition has a slight variation. This latter is given in Table1.

The characteristics of the influent don't obey to the Tunisian standard related to agricultural reuse (INNORPI, NT106.03.1989). Thus an appropriate treatment is necessary.

Physicochemical performances

The physicochemical analysis shows that during the treatment period the reduction of COD is 89% (average). The residual concentrations vary between 27 and 88 mg L^{-1}. These removal efficiencies are better than the

Table 1. Influent characteristics

	Influent	NT 106.02	NT 106.03
pH	7,91-8,25	6,5-8,5	6.5-8.5
EC (mS/cm)	5,82-6,46	-	7
SS (g/l)	0,3-1,02	0.03	0.03
COD (mg L^{-1})	431-984	90	90
BOD5 (mg L^{-1})	230	30	30
NTK (mg L^{-1})	78,4-93.2	100	-
Cu (mg L^{-1})	absent	0,5	0.5
Hg (mg L^{-1})	0.708	0.001	0.001
Pb (mg L^{-1})	0.198	0,1	1
Cr (mg L^{-1})	0.724	0,01	0,1
Ni (mg L^{-1})	0.6	0.2	0.2

NT 106.02: Tunisian standard related to the sewage discharge in the water bodies

NT 106.03: Tunisian standard related to the wastewater quality requested for agricultural reuses

reduction achieved by conventional treatment plants which don't exceed 85%.

We have recorded also a complete retention of SS by the microfiltration membrane. Our results accord with those found by (Rosenberger et al., 2002 and Khor et al., 2007; Rosenberger et al., 2002; Khor et al., 2007).

A total retention of suspended solids was recorded. The removal of TOC after treatment with the membrane bioreactor reaches 73%. The residual concentrations didn't exceed 15 mg L^{-1}. The abatement of nitrogen achieved after treatment is 88% (average).

Microbiological performances

The results shown in Table 2 prove that the capacity of microfiltration membrane in retaining microorganisms. These results concord with those of (Guo et al., 2008) which showed that 100% of bacteria and coliforms were eliminated after treatment with an MBR system.

Toxicity removal

Phytotoxicity tests were carried on. Phytotoxicity of waste water was assessed by the determination of the germination index (GI) of a very sensitive plant belonging to the family of *Cruciferae Brassicaceae* (*Brassica cernua*).

Table 2. Microbiological composition of the influent and the permeate

Micro-organism	Influent (min-max)	Permeate
Total germe (UFC/100ml)	9 10^8-60 10^8	14
Total Coliforms (UFC/100ml)	10 10^4 - 40 10^4	0
Faecal Coliforms (UFC/100ml)	34 10^3-106 10^3	0
Faecal Streptococcus (UFC/100ml)	15 10^7-450$10^7$	0
Staphylococcus	6 10^4-136 10^4	0
Pseudomonas (UFC/100ml)	0-47	0
Salmonella	present	absent
Helminth eggs (egg/T)	190-250	0
Protozoa cycst (cyct/T)	620-1100	0

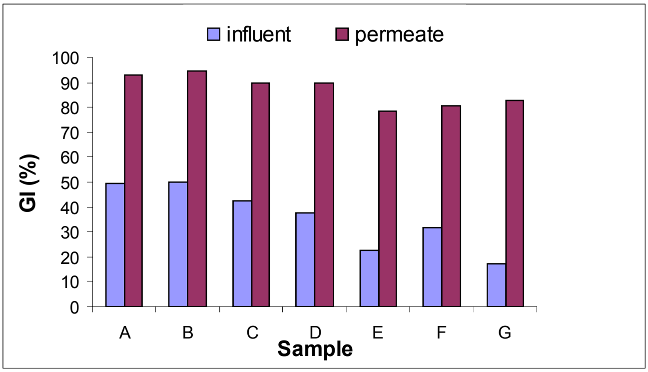

Figure 2. Germination index of the influent and the permeate

Obtained results give an idea about the improvement of the germination index (Figure 2) before and after treatment with the MBR. We note that GI don't exceed 50% in the influent while it is 86% in the permeate. That does confirm the efficiency of the MBR in the treatment of domestic wastewater.

After stabilization of removal efficiencies a second concentration of biomass was applied, we have increased the MLSS concentration from 4.5–9 g L^{-1}.

MBR performances with the second MLSS concentration

Results shows that when going from 4.5 to 9 g L^{-1} the soluble COD removal was improved and it reaches 93% (average) (Figure 3).

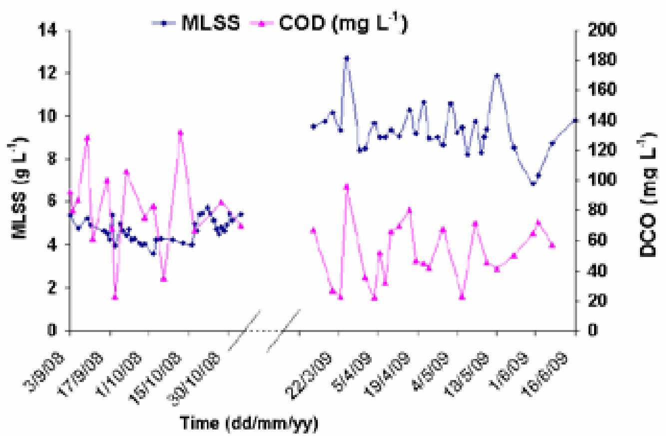

Figure 3. MLSS and COD evolution

The reduction of TOC after increasing the MLSS concentration was enhanced and it get to 90%.

The abatement of nitrogen achieved after applying the second biomass concentration is 78% (average).

Exopolymeric substances production

During this period of nine months the total concentration of EPS has a tendency to increase, it varies from 25.7 to 57.6 (average 46.8) mg/g MVS. The same speed was observed for soluble and bounded EPS. In fact, soluble EPS represent 44.1% and bounded EPS 56.75% of total EPS. With these levels of exopolymeric substances, no fouling has occurred and the reactor operates in a normal way.

The total EPS concentrations found are lower than those reported by Liu et al, (2002), they have extracted 164.9 mg / g total MVS of EPS from activated sludge taken from a municipal wastewater treatment plant.

Conclusion

The treatment of industrial and urban wastewater knows significant progress with the development of the membrane bioreactor technology. The objective of this work was to apply the technique of membrane bioreactor for treating urban wastewater using an SMBR containing a microfiltration membrane. After the start up period, the SMBR was operated with a hydraulic residence time of 24 hours, a biomass residence time of 15 days and MLSS concentration of 4.5 g L^{-1}. Under those operating conditions the removal efficiency of soluble COD, TOC, total nitrogen and SS reach respectively 89%, 73%, 88% and 100% . After stabilization of the system a second concentration of biomass was applied we increased the MLSS concentration from 4.5 to 9 g L^{-1}. A slight improvement of the different removal efficiencies was recorded. After nine months of continuous work the reactor operates with constant performances and without membrane fouling. The effluent treated by these SMBR present good physicochemical and microbiological qualities.

Acknowledgements

This work is realized under the frame work of the Puratreat Project which is an EC-funded research initiative that aims to study the application of Membrane Bioreactors as an alternative to the conventional treatment of urban wastewaters in the Southern and Eastern Mediterranean regions.

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Removing Pharmaceutical Residues from Wastewater

Damià Barceló, Jelena Radjenović, Mira Petrovic

Introduction

Once they enter a wastewater treatment plant (WWTP), pharmaceutical residues are usually not completely degraded or retained by adsorption to sludge. Hence, they pass through conventional wastewater treatment and end up in the receiving waters in certain percentage. Considering the ubiquity and pseudo-persistence of pharmaceutically active compounds (PhACs), end-of-pipe treatment of wastewater might increase the ecotoxicological risk for the environment and eventually humans. The upgrading of WWTPs and implementation of sustainable technologies impose as possible solutions for the safe reclamation of high-quality treated effluent. Advanced treatment options such as membrane bioreactor (MBR), nanofiltration (NF), reverse osmosis (RO), advanced oxidation processes (AOPs) and ozonation have been gaining attention due to the enhanced removal of PhACs from sewage and drinking water.

Elimination of pharmaceuticals by Membrane BioRectors (MBRs)

The MBR technology combines biological activated sludge process and membrane filtration for water and wastewater treatment. Due to the employment of microporous membranes for solid/liquid separation, MBR overcomes some major limitations of the conventional activated sludge (CAS) treatment such as limited sludge concentration, high sludge production, bulking sludge with poor settling characteristics.

There is still a great deal of discrepancy in literature data on the performance of MBR in removing PhACs as well as other micropollutants from wastewater. While some authors claim MBR an advanced technique for degrading more efficiently pharmaceutical residues (Göbel et al., 2007; Bernhard et al. 2007), other report comparable performances of MBR and CAS treatment (Clara et al., 2005; Kimura et al., 2005). Although MF/UF membranes act as an absolute barrier for solids in an MBR, removal of pharmaceuticals and other trace organics due to the sieving effect can be excluded. The removal of PhACs in MBR will be influenced by the same factors as during the conventional treatment of wastewater (i.e., T, pH, HRT, SRT, biomass concentration). Often, very long SRTs allowed by the configuration of MBR are indicated as responsible for the enhanced removal of specific pharmaceutical residues.

In this study, in order to evaluate conventional and advanced MBR wastewater treatment in eliminating of pharmaceutical residues, a laboratory-scale MBR working in parallel with a full-scale CAS, and two pilot-scale MBRs working in parallel with a full-scale CAS, were evaluated. Main results and conclusions are summarized below:

a. From the aspect of COD, N-NH4 and SS removal, MBR technology clearly outperforms CAS treatment affording a high quality effluent. The membrane barrier enables an efficient solid-liquid separation, where the improved COD and ammonia removal is attributed to the combination of complete particulate retention by the membrane, including suspended COD and high MW organics, as well as to the avoidance of biomass washout problems common in activated sludge systems. Consequently, stable conditions for the growth of specialized microorganisms are provided and they are able to remove slowly biodegradable components.
b. Laboratory-scale MBR operating with SRT~3 months enhanced significantly the removal of pharmaceuticals having medium degradability in full-scale CAS treatment at WWTP. For example, removal of diclofenac was enhanced from 50.1% in CAS to 87.4% in MBR; gemfibrozil was removed with only 38.8% efficiency in CAS, while in MBR 89.6% elimination was achieved. For well-degradable compounds (e.g., ibuprofen, paroxetine, naproxen, acetaminophen), as well as for the recalcitrant ones (e.g., carbamazepine), MBR and CAS had similar performances. In case of two pilot MBS (one flat sheet (FS) MBR and another with hollow fiber membranes (HF)) showed that FS experienced more stable operation at higher SRT that enabled a more efficient removal for most of the investigated drugs (e.g., ß-blockers atenolol,

sotalol, metoprolol and propranolol, hypoglycaemic agent glibenclamide, lipid regulators gemfibrozil, bezafibrate and pravastatin, anti-histamines famotidine and ranitidine, anti-inflammatory drugs propyphenazone and mefenamic acid, and antibiotics erythromycin, sulfamethoxazole, ofloxacin and trimethoprim, as shown in Figure 1), with lower fluctuations in effluent concentrations. Possibly due to frequent sludge wasting and much lower MLSS concentration, HF MBR showed worsened performance in eliminating some of the compounds (e.g., ß-blockers, anti-histaminics ranitidine and famotidine, and antibiotics erythromycin and trimethoprim). In conclusion, SRT seems to be the key operational parameter for optimizing biological wastewater treatment (CAS and MBR) for an efficient degradation of pharmaceutical residues.

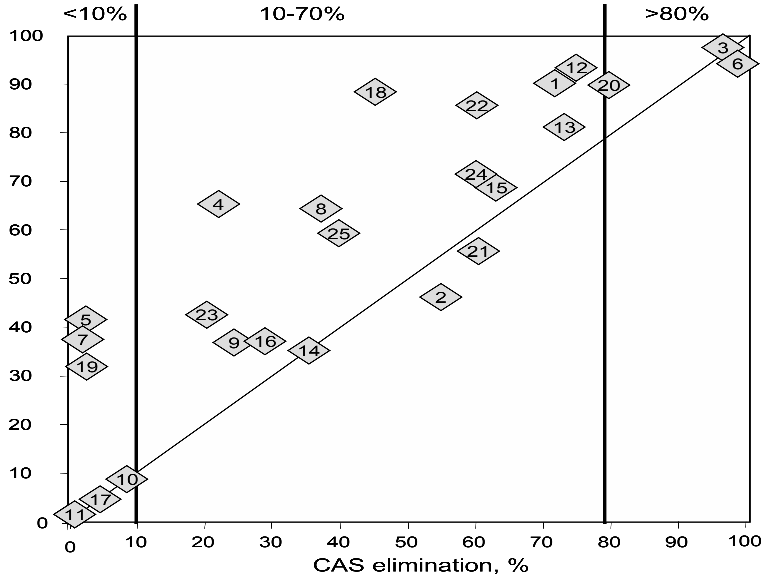

Figure 1. Comparison of the mean removals of encountered pharmaceuticals in full-scale CAS and pilot-scale MBRs. The eliminations presented for MBR are given as mean values of the removals of each compound obtained in two pilot-scale MBR (one with hollow fiber membrane and another with flat-sheets). 1) naproxen, 2) ketoprofen, 3) ibuprofen, 4) diclofenac, 5) indomethacin, 6) acetaminophen, 7) mefenamic acid, 8) propyphenazone, 9) ranitidine, 10) loratidine, 11) carbamazepine, 12) ofloxacin, 13) sulfamethoxazole, 14) erythromycin, 15) atenolol, 16) metoprolol, 17) hydrochlorothiazide, 18) glibenclamide, 19) gemfibrozil, 20) bezafibrate, 21) famotidine, 22) pravastatin, 23) sotalol, 24) propranolol, 25) trimethoprim. Modified from Radjenovic et al. (2008)

Photocatalytic processes for the removal of pharmaceuticals

The versatility of AOPs reflects in different options for production of $^{\bullet}OH$ radicals, depending on the requirements of the specific treatment. The AOPs are characterized by a variety of radical reactions that involve combinations of chemical agents (e.g., O_3, hydrogen peroxide H_2O_2, transition metals, and metal oxides) and auxiliary energy sources (e.g., UV-vis radiation, electronic current, γ-radiation and ultrasound). Other examples of AOP include H_2O_2/UV, Fenton (Fe^{2+}/H_2O_2), photo-and electro-Fenton, chelating agent assisted Fenton/photo-Fenton, heterogeneous photooxidation using titanium dioxide (TiO_2), γ-radiolysis, and sonolysis. The $^{\bullet}OH$ radicals are extraordinarily reactive species with the rate constants of reactions with the majority of organic molecules in the order of 10^6-10^9 $M^{-1}s^{-1}$. Also, their lack of selectivity is an advantage when dealing with highly contaminated waters. The major advantage of the photolytic oxidation based processes are operation at room temperature and the possibility to effectively use sunlight or near UV for irradiation, which could result in considerable economic savings especially for large-scale operations.

The photocatalyzed degradation of organic environmental pollutants in the presence of a semiconductor catalyst has become a subject of increasing interest over the last 10 years. The literature reports a variety of photocatalytic reactions involving several metal oxides such as TiO_2, ZnO, Fe_2O_3, WO_3 as well as other semiconductors (i.e., CdS). However, considering the toxicity, availability, photocorrosion resistance, catalytic efficiency and cost, TiO_2 is the preferred choice.

Besides some drawbacks of solar heterogeneous photocatalysis (e.g., necessity of real waters to be transparent in the UV-vis spectral region, slow complete mineralization of compounds having heteroatoms at low oxidation degree), it offers interesting advantages such as low cost and TiO_2 catalyst, stable of in a wide range of pH, system applicable at low concentrations, possibility of coupling with other types of water treatment (e.g., biological), and total mineralization can be achieved for most of the organic pollutants (Herrmann, 1999).

In this study two AOPs were evaluated: TiO_2 asissted and photo-Fenton photocatalysis performed at Compound parabolic collector (CPC) reactor at Plataforma Solar en Almeria, Spain. Both treatments were highly efficient in degrading selected pharmaceuticals, i.e. antipyretic drug acetaminophen, β-blocker atenolol and anti-histaminic drug ranitidine. The intermediate products identified for atenolol and ranitidine were formed concomitantly with the disappearance of the parent compounds (i.e., as primary intermediates), and were rapidly degraded. Carboxylic acids were detected at the end of TiO_2 and photo-Fenton degradation for all three compounds, demonstrating that both parent compounds and transformation products (TPs) are finally degraded to organic short-chain acids before being mineralized. Therefore, treatment time should be enough to produce such compounds, but complete mineralization is not necessary. Lower reaction rates for synthetic effluent compared with distilled water were observed in all cases, mainly due to the detrimental effect of other organic compounds typically present in municipal wastewater effluents.

Acetaminophen and atenolol were degraded completely in TiO_2 and photo-Fenton solar photocatalysis, following pseudo-first order reaction kinetics. Photo-Fenton treatment seemed to be more efficient that the TiO_2 photocatalysis. The pathways of photocatalytic degradation of atenolol in both TiO_2 and photo-Fenton process start •OH radical attack at alkyl side-chain and amide moiety, with further oxidation either by •OH radicals or by O_2 (Figure 2).

Ranitidine was also completely degraded following pseudo.first order reaction kinetics, as shown in Figure 3. However, it was degraded at similar rate in TiO_2 and photo-Fenton process, probably because of the incapability of ranitidine to form hydroquinone moieties that enhance the decomposition during Fenton reactions and due to its high adsorption on TiO_2 surface. The pathways of the photocatalytic degradation of ranitidine in both TiO_2 and photo-Fenton processes start with hydroxylation (i.e., •OH radical attack), dealklylation, deamination, oxidation by •OH radicals and O_2 and reduction by conductive band electrons. It can be assumed that cleavage of furan ring will take place, while different aliphatic products are subsequently formed before complete mineralization.

Conclusions

Urbanization and constant population growth is likely to keep increasing the quantity of wastewater discharged to WWTPs. Also, considering fast development of pharmaceutical industry and general aging of population,

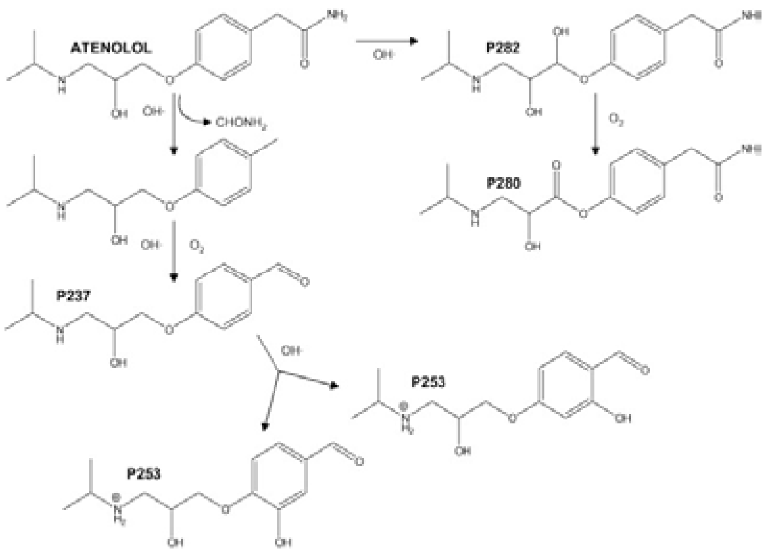

Figure 2. Proposed photocatalytic degradation pathway of atenolol in aqueous solution by solar TiO_2 and photo-Fenton treatment. Modified from Radjenovic et al., 2009

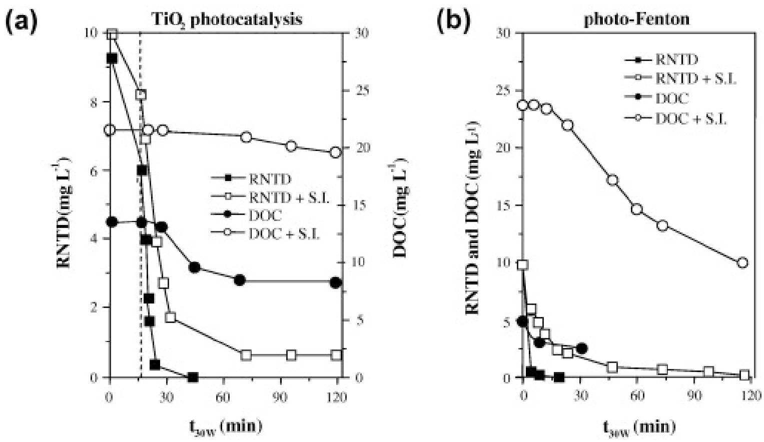

Figure 3. Degradation and mineralization of ranitidine by: a) TiO2 photocatalysis, and b) photo-Fenton experiments. (Modified from Radjenovic et al., 2010)

it can be assumed that PhACs will be more consumed and with a more diverse array, with development of new compounds that have unknown fate and effects on the environment. At the same time, the demand for clean water steps-up as well.

The processing of wastewater in municipal WWTPs cannot prevent the entry of PhACs into surface water, because of high stability of some compounds and their metabolites against biological degradation. Advanced technologies, such as MBR and AOPs, have proven to be more efficient in the elimination of various classes of organic compounds, among which pharmaceutical residues as well. Although the efficiency of some technologies and their economic feasibility cost in removing micropollutants such as PhACs is still not clear, they seems as a promising mean for their removal.

Acknowledgments

This material is based upon work supported by the Spanish Ministry of Science and Innovation through the projects SCARCE (Consolider-Ingenio 2010 CSD2009–00065) and CEMAGUA (CGL2007–64551/HID).

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8

NEW THRUSTS IN ENERGY AND CLIMATE CHANGE

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Climate Change Treaties: Can the UN help?

Robert J. Berg

In this note, I suggest that UN leadership on climate change is indispensable, but not in the way the UN and its members now see it. Whether or not a formal agreement of a meaningful nature is achieved to succeed the Kyoto Treaty, the UN can have far more impact by walking the walk, not just talking the talk.

Why achieving meaningful agreement is hard and unlikely

The UN is the focal point of international negotiations to reduce greenhouse gases. This in itself is a default position. Many informed observers of international negotiations say that success on a successor to the Kyoto Protocol could only come about if the US and China reached an agreement, and that would be possible only if the US actually earned the right to negotiate from strength, e.g., if it passed meaningful climate change legislation. Like falling dominos, the theory went, if the US and China agreed, next to come would be the EU, Russia, Brazil, and, if lucky, India. Once an agreement had been reached with these main parties, coming to the UN to obtain a global agreement would make sense, as has most often been the case of the greatest negotiating successes. Pre-negotiate and then use the big stage for the signing ceremony. But the US domino didn't fall, and, perhaps consequently, none of the other big dominos fell. Instead, the UN lost face proclaiming a 'Seal the Deal' campaign in the run up to Copenhagen, even though there was no deal to seal. Now the UN operates from a weakened position as it struggles with a new team to put a deal together.

Maybe we have been too optimistic about the possibility of a comprehensive global deal on climate change. While the UN has been associated with great success in some climate-related negotiations, it is worth comparing how daunting the current negotiating task really is. The treaty that led to the elimination of the ozone hole was perhaps the most successful of the UN-brokered climate treaties.

What is remarkable about the ozone treaty is that the science was clear: one chemical had been clearly traced to creating depletion of the ozone layer. CFCs were used by a group of easily identifiable, mainly larger manufacturers in a few industries. A replacement for that chemical was available and viable. National legislation was feasible and doable to ban the use of CFCs. Thus follow up at the national and industrial levels, while not without challenges, could be relatively straightforward. It helped, of course, that the negotiators created peer review mechanisms for the affected industries and other means that cleverly managed the situation in remarkably short order.

Compare the challenges to moderate greenhouse gases. The science is pretty good on the sources of greenhouse gases. Most of the ingredients of the atmospheric soup are known, but their individual and particularly their collective interactions are still being learned. Shindell and colleagues at NASA's Goddard Institute for Space Studies see carbon dioxide responsible for 43% of man-made warming, methane 27%, black carbon 12%, halocarbons 8% and carbon monoxide and volatile organics 7%, each with their own dynamic and remedies. (See Drew T. Shindell, et. al. 'Improving Attribution of Climate Forcing to Emissions' *Science*, 30 October 2009, Vol. 326 , No. 5953, pp. 716–718.)

If there are still things to learn about the causes of global warming, the field of mitigating actions is even more complex and is quickly evolving with new options surfacing regularly. The main focus of mitigation has been to reduce CO_2 emissions from the main users of fossil fuels: power plants and vehicles. But look at the range of remedies that Al Gore talks about: reducing forest fires (a source of more CO_2 than all the world's vehicles), reducing land tilling, use of biochar, renewables, smart buildings, smart cities, smart economies, and a slew of other new scientific solutions. Together, these remedies rightly call for a different lifestyle for the great majority of the world's people. They imply the need for re-educating most of the world's adults and educating children differently than almost all are educated today so that we create consumers who strongly prefer sustainable lifestyles. And implied but rarely spoken about, because it has become politically unpopular, getting far more serious about population planning. This is just the mitigation side. The adaptation side is equally complex and ambitious; think just of what might well be needed to safeguard coastal cities and estuaries from rising oceans and storm surges damming the Mediterranean and the like.

What this means is that any reasonable agreement on coping with greenhouse gases will need to cover interests across our societies and involve nearly everybody. A single treaty, adjustable as new scientific findings and solutions emerge, cannot do this. Moreover, the ability to monitor and pressure for compliance of numerous actions across the globe will be well beyond existing international authorities.

Is the whole endeavor hopeless? No. but we ought to heed the advice of the late Martin Landau 'Redundancy, Rationality, and the Problem of Duplication and Overlap.' Public Administration Review 29 (July–August 1969): 346–358.) that the more important the problem, the more strategies, even overlapping and duplicative strategies and programs, are needed.

The strategies the UN has adopted regarding climate change focus on promoting treaties and their enforcement, indexing (e.g., the IPCC), and policy research. They have raised awareness of complex, inter-related issues, but have not enabled the UN to perform the kind of leadership role that is necessary to effect real change.

Walking the walk and why is it important

At the topmost ranks of the UN, the range of problems being faced is almost endless. Top policy people will tell you they spend the morning on the global economy, lunch on the climate, the afternoon on hot spots, along with numerous interruptions to cope with internal and external 'crises.' Climate is just one of the hot potatoes being juggled. As a 'system,' the UN's work on climate and the environment is seriously fragmented. UNEP, created to coordinate the UN's work on environment, does no such thing. In contrast are the three main priorities of the UN: development, peace and human rights (in that order), where priorities and assignments are pretty well organized. Judging by its own actions it is hard to tell that, as the

UN often says, that the challenge of climate change and an accompanying unsustainable lifestyle is truly the top priority facing the world.

The rationale for making the nexus of climate, environment and development—sustainable development—the UN's top priority extends across the UN's mandates: growing numbers of environmental refugees, looming conflicts over water rights, challenges to development performance, food security threats particularly where there is high population growth, and the need to reconfigure infrastructure in poor countries, all will call for the UN to respond. Yet even if climate/environmental sustainability were well integrated in the UN's core programs, the UN can only do so much. It controls a modest amount of human and financial resources in comparison with nation states. For example, the number of UN staff and UN peacekeepers combined is 0.3% of China's government payroll.

The preponderant share of important decisions and actions on environmental matters, including climate change, have been and will continue to be managed at the national level where the rationale for actions will be domestic.

All nations will face a long term governance crisis due to our emerging environmental crisis. We have few parallels for such emergencies. Wars are shorter term propositions.

The lessons on how nations can best manage the looming environmental crisis brought on by climate change can be found in a composite history of the best cases of management of HIV/AIDS in countries heavily impacted by that epidemic. As heads of state became convinced that HIV/AIDS was a crisis, they turned to their minister of health, a mid-level official in terms of cabinet rank, to cope with the disease. But as the impacts and prevention strategies became better understood, it turned out that every major part of government (and civil society) also should have important responsibilities. The ministry of defense had to teach troops safe sex. The ministry of agriculture had to find low labor agriculture for families and communities where only grandparents and children were left to farm. The ministry of industry had to help companies adjust to high sickness and death among their employees and customers. The religious authorities had to understand the role of traditional healers in managing death. The ministry of education needed to teach safe sex and cope with huge teacher losses. And the ministry of justice had to redouble efforts to safeguard women and girls. In fact, HIV/AIDS required a government-wide response and coordination at the highest levels, far beyond the ability and power of the ministry of health.

Now comes climate change dramatizing the need for sustainable development. The temptation is to approach the minister of environment (if that position exists) and turn over the problem to that official. That minister, sits at the far end of the cabinet table, likely has very little access to the head of state, and is in fact situated much as UNEP is in the UN. Only in recent years has UNEP been admitted to the biannual meetings of heads of UN agencies.

Coping with climate change in a long term sense, i.e., sustainable development, will need an approach to national governance that mobilizes all parts of government. Enlightened national leaderships will need to ask each minister and head of agency to do different long term major tasks, to augment or delete current work, to shift from governance seeking high growth to governance for sustainable development.

And where does such a model of enlightened governance exist? Alas, the answer is it is rare, and more often found in bits and pieces than as a whole. And that is why the UN has such crucial potential. It can model what national governments need to do. And it would do so by a system-wide initiative.

Having proposed and co-authored the UN's first system-wide substantive initiative (aimed at helping Africa), I am a bit partial to this approach. Although that initiative failed in its implementation, the model of cooperating across the UN system proved interesting enough to be deployed in the UN's current work on the Millennium Development Goals where there is a considerable amount of cooperation and good implementation among agencies. The UN is increasingly trying to manage itself as a system, as opposed to a seemingly random collection of entities.

What is the potential of a UN-System Wide Initiative on Sustainable Development? It is actually quite large. Programs could be far better focused to respond to the needs. For example at the UNDP, a quarter of their program promotes better governance (accountability, transparency, popular participation) and an additional 8% finances a scattering of environmental programs. UNDP could consolidate those accounts to become the premier source of fostering governance for sustainable development, which for political and economic purposes should be recast as 'sustainable growth.' A feature of that program could be helping top national leaders (chefs du cabinet, for example) learn how to coordinate long term cross-governance initiatives, maintain a sense of urgency and provide a stream of political benefits from work on climate change/sustainable development. UNESCO could ramp up its efforts on educating for sustainable development by working directly with education ministries to foster new generations of consumers who create demand for products fit for sustainable economies. FAO could help national agricultural systems adjust to new agricultural realities. The World Bank (a cooperator with the UN, but not a UN agency) could elevate its environmental and sustainable development work on par with the International Finance Corporation. Both would then be headed by an Executive Vice President, thus equating sustainability to be as important as profit. Even the International Postal Union could help countries create long-term educational campaigns on sustainable development using stamps. And so forth around the UN cabinet table.

A system-wide response would also highlight two major gaps in the multilateral system: we have no global groupings tasked with water issues nor energy issues. Solutions must be found.

There are three unique advantages of a well designed UN system-wide initiative:

1. The UN would show by example what national governments need to do and this would raise the UN's credibility on environmental issues as a venue for negotiations and as a public pressure point for change.
2. Each UN agency convenes global meetings in its ministerial line, thus part of the initiative would be to raise climate change/sustainable development issues in each such meeting. There has never been a coordinated effort by the UN to use its power of convening for focused global purpose. The potential impact could well be enormous.
3. The UN teaches countries by peer reviews and peer pressures, thus it would index national behavior in numerous climate and sustainability areas, highlight best cases and foster peer learning among states. This should be a normal function of each major UN entity.

In all of this the sequences are important. Climate change is both the greatest threat to sustainable or any other kind of development and the most urgent matter to address across the UN system. It may well be that we are too late and that geo-engineering solutions will have to be contemplated and instituted. But in the meantime before such a drastic approach is taken, every possible step must be undertaken to reduce greenhouse gases and the

UN must move into emergency mode across its system of organizations. Helping countries and peoples moderate the warming of the earth will be the largest challenge ever to face the UN.

Naturally there are serious implications of these proposals for UN leaderships at agency and headquarters levels. One can't expect overnight miracles. But at the least, the UN will need well placed high level advisors who have scientific and political credibility, very broad vision, who can inspire the top leaders to have the requisite courage, and can help in very creative ways to work with civil society around the world to create pressure at the national level for backing these proposals in the UN General Assembly. The UN will also have to show leadership with the public and in so doing it should call upon its main personal financial backer, Ted Turner, to help mobilize global public opinion in concert with the UN's system-wide initiative. The initiative could be the rationale for a long overdue re-tooling of the various modest public affairs entities of the UN, along the lines of UNICEF's effective public affairs establishment.

In the end, the question is how the UN can best help stimulate the requisite national actions required to save the world from catastrophic warming. Searching for the hard power of treaties in the hope that they will be enforceable is one way, and must be pursued. But I would place my bets on a multi-pronged approach to encourage national governments more directly to take the necessary fundamental actions.

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Climate Change Effects in Northern Egypt

U. Cubasch and I. Höschel

The North of Egypt and particularly the Nile delta has been identified by the Intergovernmental Panel on Climate Change as among the hotspots of vulnerability. Ensemble model calculations project a temperature rise of about 3.2°C for the intermediate IPCC SRES A1b scenario, which is higher than the global average projections by IPCC. Precipitation is expected to decline by about 20%. This can partially be compensated for by changing farming practices and water management. Under the European Union's proposals to limit global warming to 2°C by the middle of this century, the temperature increase in Northern Egypt will stay at around 2°C and average precipitation is expected to remain at present-day values.

A sea level rise of 1m will adversely affect about 10% of Egypt's population. Simulations with a regional ocean-atmosphere model for the Mediterranean sea, however, predict very little sea level rise during the next century, since any thermal expansion from higher temperatures will be compensated for by increased evaporation due to the warming. Changes to the Nile delta topography due to the extraction of natural gas underneath complicates the estimate of sea-level change even further.

Introduction

The North of Egypt has attracted a lot of attention since in the IPCC-Report WG II (2007) the Nile was mentioned as a potential hotspot of vulnerability. It is assumed that by the year 2050 more than 1 million people will be affected by climate change. The Mediterranean region in general has been identified as being in future severely affected by climate change.

Therefore a number of studies have been carried out within the framework of EU-projects to investigate climate change and its impact in this region. This paper will give a brief overview on this projected climate change. It will focus on near-surface temperature, precipitation and sea-level change. Projections of temperature and precipitation have been carried out using a multi-model ensemble of European climate models within the EU-Project ENSEMBLES.

Model Experiments

Climate projections were simulated by eight coupled atmosphere-ocean-general-circulation models (AOGCM) for two scenarios. The details of these models are given in Table 1. A comprehensive description of the models and global results can be found in Johns et al. 2010.

Table 1. AOGCMs with the horizontal and vertical resolution of the atmosphere and ocean components, references and country of origin.

Model	Atmosphere	Ocean	Reference	Country of Origin
CNRM-CM3.3	T63L31	2°L31	Salas-Meliaet al. 2005	France
ECHAM5-C	T31L19	3°L40	Roeckner et al. 2010	Germany
EGMAM2	T30L39	0.5/2.8°L20	Huebener et al. 2009	Germany
INGVCE	T31L19	2°L31	Fogli et al. 2009	Italy
IPSL-CM4	N84L19	2°L31	Marti et al. 2009	France
HadGEM2-AO	N96L38	1°L40	Collins et al. 2008	UK
HadCM3C	N48L38	1.25°L20	Booth et al. 2009	UK
BCM2(C)	T63L19	2.4°L35	Furevik et al. 2003	Norway

All the models have been run for the IPCC SRES A1b scenario, which assumes a continuous increase in greenhouse gas concentrations during the 21st century; and a mitigation scenario E1, which is based on the assumption that greenhouse gases are expected to stabilize during the middle of the 21st century. It was developed with the Integrated Assessment

Model IMAGE 2.4 starting from emission scenario A1b (Nakicenovic et al. 2000) as baseline scenario to reach the EU prescribed 2 °C-target (Lowe et al. 2009, Van Vuuren et al. 2007). The greenhouse-gas concentrations reach a maximum about 530 ppmv CO_2–equivalent in the mid of the 21st century and decrease gradually to 450 ppmv afterwards.

With the models, 36 simulations have been performed from years 2000 to 2100 for the emission scenario A1b, a scenario without any mitigation policy and for the EU scenario E1 for the region Northern Egypt (25E - 35E, 27.5N–32.5N).

Temperature Change

During the next 100 years global mean temperatures are expected to rise between 1 to 4 °C depending on the scenario (IPCC, 2007). The A1b scenario is projected to generate a global mean temperature rise of 2.8 °C. In the Mediterranean Region the temperature rise will be rather higher than the global mean because the dry conditions amplify the warming. For the North Egyptian region the temperature increase will exceed 3.2 °C by the end of the 21st century (Figure 1a). If, however, the EU-suggested limit of global mean temperatures stays below 2°C, the temperature in Northern Egypt will not exceed this value either (Figure 1b).

Precipitation Change

According to the IPCC WGI report the precipitation amount in the Mediterranean region is expected to decrease generally during the next 100 years. The EU ensemble simulations for the scenario A1b indicate that particularly North Africa will experience a considerable drop in precipitation. For Northern Egypt the precipitation amount is expected to decline by about 20% (Figure 2a) for the scenario A1b, but does not change significantly in the stabilization scenario E1 (Figure 2b).

Sea-level Change

Relative sea level can change through the following factors: a) by thermal expansion of the water b) by a changed water supply e.g. by melting of glaciers and ice sheets (Antarctica, Greenland), c) by changed precipitation

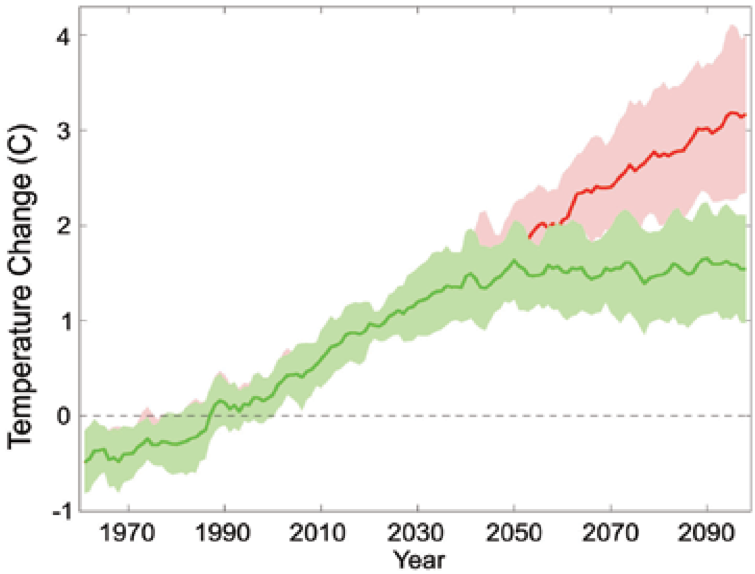
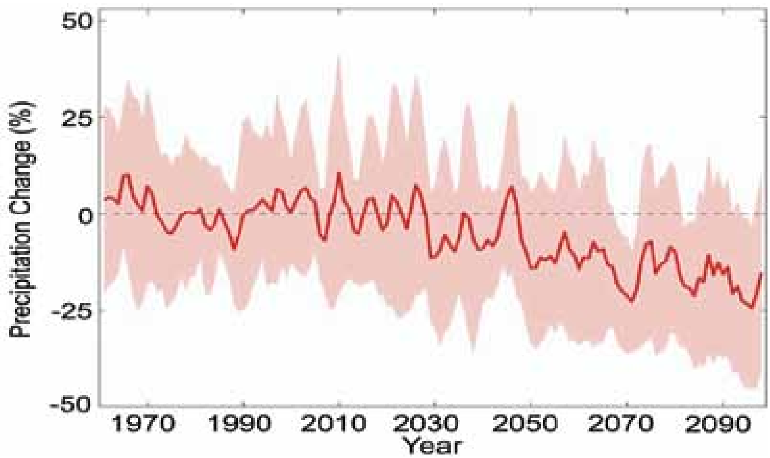


Figure 1. The temperature change relative to the 1980–1999 average for Northern Egypt for the IPCC SRES scenario A1b to be darker and for the EU scenario E1 to be lighter. Shaded areas indicate the spread in the projections by the 18 model runs

and evaporation; d) by dynamical effects due to the shift of oceanic currents and e) by vertical movements of the topography. The Nile delta is particularly vulnerable to sea level changes due to its low lying topography.

IPCC WG I projects a global mean sea level rise from 10 cm to 42 cm by the end of the 21st century, depending on the scenario. For scenario A1b one would obtain a global sea level rise of 32 cm, which would increase the vulnerability of the Nile delta (IPCC WG II, 2007). The long term effects of sea-level rise are more dramatic: it continues due to the thermal inertia of the oceans to more than 3 m within the next 1000 years, which would affect about 25% of Egypt's population (Dasgupta et al. 2007). Changed storm surge intensity can have a negative impact on the Nile delta as well, particularly, if the mean sea level has risen.

However, local effects have to be taken into consideration as well. The Mediterranean is a sea which can only be supplied with water through the strait of Gibraltar. The projected temperature rise results in an increased evaporation resulting in a lowering of the sea level, which can only be



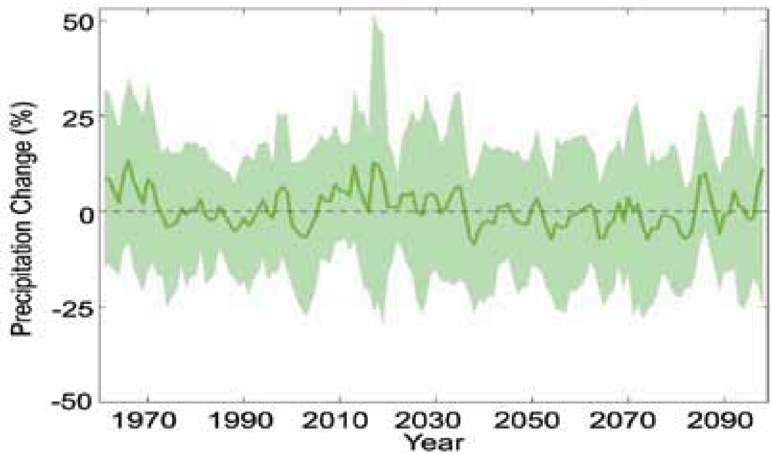


Figure 2. The precipitation change for Northern Egypt: (top) for the IPCC SRES scenario A1b and (bottom) for the EU scenario E1. Shaded areas indicate the spread in the projections by the 18 model runs.

compensated by an additional through flow through the narrow strait of Gibraltar. (Tsimplis et. al. 2008) calculated the Mediterranean sea-level change using an Atmosphere Ocean Regional Model. They find that the sea level in the Mediterranean is rising by a maximum of 35 cm for the IPCC A2 scenario (which is a higher scenario than the A1b scenario). For the Nile Delta, however, they calculate a sea level rise below 2 cm for the next 100 years due to the effects of increased evaporation and sea water dynamics.

An additional effect not considered here is the extraction of natural gas from underneath the Nile delta, which lowers the topography relative to the sea level.

Conclusions

Northern Egypt will experience the effects of climate change in several ways: for the scenario A1b the temperature will increase more than the global average and precipitation will decrease. A study by Giannakopoulous (2009) suggests that agriculture will feel negative impacts in all types of crops. They point out that some of the negative impact can be compensated for by an appropriate selection of crops. Assuming the target of limiting global warming to 2 °C is reached, the impact of climate change on Northern Egypt for the next 100 years will not be that severe. Precipitation will stay at its present day averages and the temperature rise will be limited to about 2 °C.

The information on sea level change is contradictory. IPCC WG II (2007) identifies the Nile delta as a potential hot spot for vulnerability. A1m sea-level rise will impact about 10% of the population (Dasgupta et al. 2007). However, physical reasons and simulations with regional ocean-atmosphere model indicate a rather modest sea level change well below this amount. Furthermore, information is lacking to which extend the extraction of natural gas from underneath the Nile delta lowers the coast line. Further research is therefore recommended in this very sensitive topic before decisions on adaptive measures are taken.

Acknowledgements

The ENSEMBLES data used in this work was funded by the EU FP6 Integrated Project ENSEMBLES (Contract number 505539) whose support is gratefully acknowledged.

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The Desertec Concept

Hani El Nokraschy

Mankind faces unprecedented challenges: climate change, population growth far beyond Earth's present carrying capacity, the global striving for prosperity, and increasing demands for energy and water. Two centuries of global industrialization has resulted in an unparalleled standard of living and an increased life expectancy for part of the world's population. However, all this has been and is still being achieved at a price: alarming environmental destruction as well as climate change which can no longer be ignored. These things will mean dramatic changes to life on Earth in the future. The Sun offers more than a ray of light: Within six hours, the world's deserts receive more energy than the total world consumption in a year. The only question we have to answer is: How can this radiant energy be economically transformed into useful energy and transported to consumers? The Desertec concept offers one possible solution

Introduction

By 2050, around 10 billion people will inhabit the Earth. And they will want to provide themselves with food, water, energy and other necessities. Yet, even today, one third of the world's population has only limited access to the basics of living; many others have even less. On the basis of current economic conditions, it will be impossible for economically-leading nations to maintain or even increase their level of prosperity while, at the same time, several billion people are left to pursue a comparable level of prosperity. Conflicts regarding access to natural resources—in particular water and energy—will be aggravated, changes in the climate will accelerate and the prerequisites of life for a majority of the world's population will be in serious danger. In view of these alarming possibilities, the main question today may no longer be whether or when we will begin to reduce the strain on Earth. It should, instead, be: How can we reduce the strain on the Earth starting from today so that:

- In 40 years, up to 10 billion people will be provided with sufficient food, water and energy
- Adaptation and mitigation of global warming can happen
- North and south of the equator, deserts span the Earth. Over 90% of the world's population could be supplied with clean power from deserts by using technologies that are available today.

Problems Associated With Global Development

Modern economies are based mainly on fossil fuels. Within an unusually short pace of time (from a geological point of view), the combustion of these fuels has led to a significant increase in the concentration of CO_2 in the atmosphere. This is the undisputed cause for increases in global temperatures and changes in the world's climate that are now in progress.

Meanwhile, more than 6.5 billion people consume far more natural resources and produce far more pollution than the Earth can accommodate. The human population's so-called ecological footprint is already larger than the Earth can sustain. The average temperature rise in the atmosphere, the melting of the polar ice caps as well as the increase in extreme weather events worldwide are obvious signs that we are putting too great a strain on the Earth. If we do not change our behaviour with determination and stop the accumulation of CO_2 in the atmosphere, we will be faced with disastrous consequences. The melting of the Greenland ice sheet, for instance, would lead to an increase in sea level of several metres. As a consequence, many areas would be flooded and would thus become uninhabitable. Other areas would be too arid to live in. These two phenomena—flooding and desertification—would spark off mass migration on an unprecedented scale.

Clean Energy is available in Abundance

The DESERTEC Concept provides a solution to this and, in doing so, it tackles efficiently all the global challenges of the upcoming decades mentioned before: shortage of energy, water and food as well as excessive releases of CO_2. At the same time, this concept offers new options for the prosperity and development of regions that have so far, from an economic point of view, been scarcely developed – as well as promising new opportunities for the economically leading countries.

Studies by the German Aerospace Center (DLR) show that, within 40 years, solar thermal power plants in particular will be capable of generating economically more than half of the electricity needs of the EUMENA region (Europe, the Middle East, North Africa) at that time.

In order to meet today's global power demand of 18,000 TWh/year, it would suffice to equip about three thousandths of the world's deserts (about 90,000 km^2) with solar collectors of solar thermal power plants. About 20 m^2 of desert would be enough to meet the individual power demand of one human being day and night – all this absolutely CO_2 free. Given the political will, it would be possible to achieve a worldwide realisation of the DESERTEC Concept in less than 30 years.

The Desertec Concept: Wind—Csp And Hvdc—Sustainable And Ready For Use

The DESERTEC concept will allow most people in the world to access solar and wind power from the energy-rich desert areas. This would be a useful addition to the renewable energy resources of each region. By using High-Voltage Direct Current transmission lines (HVDC), it is possible to transfer power with losses of about three percent per 1,000 km. Given the relatively high intensity of sunlight in desert regions and the relatively small variations between summer and winter, the benefits of generating electricity in desert regions will more than outweigh the cost of long-distance transmission. More than 90% of the people in the world live within 3000 km of a desert and may be supplied with solar electricity from there.

Concentrating Solar-Thermal Power Plants (CSP-Plants) have some technical advantages over photovoltaic (PV); Sunlight is concentrated to create heat, which may be used directly to generate steam and drive a turbine, or it may be stored cheaply and efficiently. Steam can then be generated at night from stored heat, and CSP plants can generate power also at night or when clouds are passing through. Gas or bio-fuels may be used as a stop-gap source of heat when there is not enough sun on cloudy days. These things mean that CSP plants can normally deliver power on demand whenever it is required.

Figure 1 Area needed to deliver solar electricity for the whole world

This ability to respond flexibly to peaks or troughs in demand is invaluable in maintaining the stability of power grids. Without that kind of facility, variable sources of power such as wind farms and photovoltaic may need to be backed up by supplies from conventional power plants (coal-fired, gas-fired and nuclear power plants), from pumped storage power plants (which are not widely available), or from relatively inefficient and expensive power storage devices.

Practical Points of View

Solar-thermal power plants have been in use commercially for two decades in the deserts of California (USA). The first plants have been operating in Kramer Junction in California since the mid-1980s and new plants have come on stream recently in Spain and Nevada. With the right framework of laws and regulations, the development of CSP plants may be ramped up fast. Also, HVDC transmission lines have been in commercial use for decades and manufacturing capacity may be expanded as required.

There are two important features of HVDC transmission lines that will help win their acceptance by the public: Firstly, HVDC transmission lines, by contrast with HVAC lines, produce hardly any electro smog. Secondly, for a relatively small increase in cost compared with overhead lines, it is possible to lay HVDC transmission lines under ground or underwater, thus minimizing their visual impact and speeding up planning applications

At present, the cost of power generated by solar-thermal power plants including its transport via HVDC transmission lines amounts to 10 to 20 euro cent per kilowatt-hour - depending on the location, technology and form of operation. However, these costs will drop significantly with economies of scales and refinements in the technologies. Moreover, there are no additional costs, often hidden from view, that arise from damage to the environment and waste disposal, as is common with fossil or nuclear power plants. It is likely that, when environmental and hidden costs are factored in, electricity from CSP plants is already cheaper than electricity from coal-fired or nuclear power plants.

DESERTEC Connects: A Concept for The EUMENA Region

The EUMENA region (Europe, the Middle East, North Africa) can profit to a great extent from realizing the DESERTEC Concept. Imagine the following scenario: on favorable sites, countries on the Southern and Eastern shores of the Mediterranean sea, including the Arabian Peninsula, would meet most of their soaring power requirements from solar power plants in deserts, supplemented by wind and hydro power. In addition, they would produce energy for urgently needed desalination of sea water and they would generate export earnings for the foreseeable future by supplying power to Europe.

The development and trading of energy from renewable sources will boost economic development in these regions and creates local jobs in the production of collectors as well as in the construction of solar power plants: For example, the construction of only one 250 MW parabolic trough power plant requires 1,000 workers and engineers for a period of two to three years. In this way, MENA countries including those with oil and gas resources, may establish a new economy with new jobs and a reduction in the brain drain. In turn, the European states will achieve their goals of reducing CO_2 emissions relatively quickly and relatively cheaply, since CSP imports provide a good substitute for power from fossil fuels. As a result, the whole of EUMENA would benefit from the trade in clean power from deserts.

Solar Power Imports and Security of Supply–Exemplified By Europe

Energy security needs to be taken seriously. It is important to point out that the DESERTEC concept does not rely exclusively on power from deserts—that source of energy is merely one of a range of renewable sources of power. By importing clean power from deserts, European countries could increase their range of renewable energy sources and thus reduce their dependence on imports of fossil fuels such as natural gas and coal. Instead of relying on relatively few large 'mega transmission lines' that are the rule with oil and gas supplies, it would be possible under the DESERTEC scenario to increase security by obtaining supplies via a relatively large number of medium-capacity transmission lines. Damage to power plants and transmission lines can be repaired easily. The system has sufficient redundancy to compensate for any failure related breakdowns of transmission lines. An orchestrated suspension of power supplies would lead to a loss of income in the producing countries – as opposed to the case with fossil energies which can be saved and sold later, and perhaps at a higher price. Beyond that, producers would lose the confidence of their costumers and future investors with such a boycott and thus do damage to themselves.

Additional Benefit: Drinking Water Through Desalination

Another motivation for developing CSP is the growing threat of shortages of potable water in arid regions. Waste heat from solar-thermal power plants may be used to desalinate sea water in plants near the sea. Thus supplies of clean drinking water may come as a bonus with the generation of clean power. Another interesting possibility is to use the shaded areas under solar collectors for growing plants, protected from the harshness of direct tropical sunlight and with supplies of fresh water provided by desalination of sea water.

Focus EUMENA

An effective political framework provides three things: It offers investment incentives to potential investors and operating companies, it ensures long-term stability in planning, and it creates transparency in markets.

There is a need for a single market in electricity throughout the EUMENA region so that, for example, any customer in Germany or the UK may buy electricity directly from any supplier in North Africa or the Middle East. To facilitate the efficient operation of that single market, there is a need for a new high-voltage direct-current transmission (HVDC) grid throughout the EUMENA region. However, with some modest upgrading of the existing grid to remove bottlenecks, the trading of electricity throughout EUMENA may begin quite soon. As volumes increase, transmission capacities may be increased by converting HVAC lines to HVDC, by building new HVDC lines, and by the installation of smart electronics.

The DLR has estimated that the cost of 20 transmission lines of five GW each would be approximately 45 billion Euros.

By means of appropriate feed-in tariffs, solar power from deserts can be made competitive with immediate effect. These instruments have proved to be successful in Germany and Spain. The need for this kind support will be reduced or eliminated if subsidies for coal-fired and nuclear electricity are removed, if their environmental and hidden costs are fully internalized, and if the current upward trend in their costs continues into the future. Meanwhile, the cost of CSP is likely to fall with refinements in the technologies and economies of scale.

Other kinds of support could be useful to speed up the construction of grids and power plants: for example, support of investments via moneys raised from the auctioning of emission certificates or from public investment programs for climate protection that are yet to be created, or via government guarantees on investments in foreign countries.

It has already been accepted that imports of renewable energy into the EU would count towards the target of 20% of European energy coming from renewable sources by 2020. A logical next step would be to introduce further feed-in tariffs in European countries that apply to imports of solar power from the MENA region.

In the future, in the interests of fair competition, the price of energy from fossil fuels must include charges for CO_2 emissions – something that has not yet been properly achieved by the European Emissions Trading Scheme. With proper charges for CO_2 emissions, solar and other renewable sources of energy would be competitive even today.

In any case, overt and hidden subsidies for non-sustainable energy sources have to be done away with, as they give incentives for damaging investments. Every year, about several hundred billion US dollars pass into subsidies for energy production from fossil or nuclear energy sources worldwide.

Those who hold on to fossil energy sources with the argument of securing jobs overlook the fact that even more jobs could be created in the new renewable industries, where consumption of fossil resources is replaced by manufacturing of equipment.

Opportunities and Prospects

Transition to clean sources of energy will make great demands on many companies but, at the same time, it will create great opportunities. Even companies with business models that are focussed on the provision and use of fossil fuels can benefit from these new developments.

DESERTEC will be especially beneficial to companies that:

- conceive, design or produce solar-thermal power plants and HVDC transmission lines
- are looking for sustainable investment opportunities in the infrastructural sector
- consume large amounts of power or are engaged in energy-intensive industries, and wish to have access to clean power at stable prices
- conceive, design or produce sea-water desalination plants
- produce or use hydrogen, and wish to reduce or eliminate emissions of CO_2
- are looking for sustainable possibilities in order to extend the scope of their business

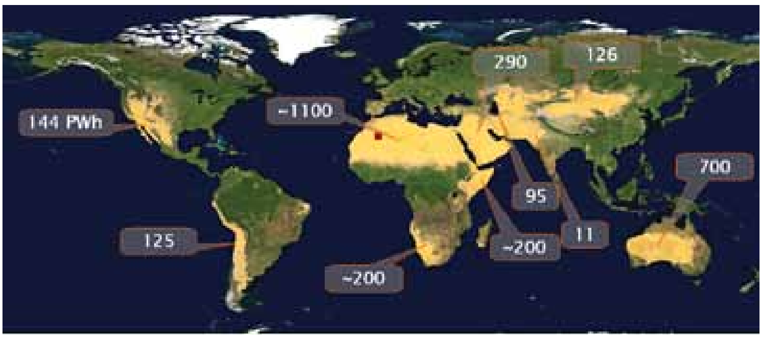

Figure 2. Annual economic potential, in PWh (= 1000 TWh). Total desert potential = 3000 PWh/y Global demand (2008): 18 PWh/y Source: Trieb et.al.,DLR, 2009

Conclusion

The expected increase of population up to 10 billion humans in 2050 is a real threat in terms of demand on energy, water and food. This can cause political destabilization in many regions of the world that may lead to serious conflicts.

An international 'DESERTEC Program' is a major opportunity to secure a sustainable future for mankind, using the abundant wind and sun resources in the deserts – which are scarcely used – offers a practicable and feasible solution to provide electricity and water. By using High-Voltage Direct Current transmission lines (HVDC), it is possible to transfer power with losses of about three percent per 1,000 km. Given the relatively high intensity of sunlight in desert regions and the relatively small variations between summer and winter, the benefits of generating electricity in desert regions will more than outweigh the cost of long-distance transmission. More than 90% of the people in the world live within 3000 km of a desert and may be supplied with solar electricity from there.

Concentrating Solar-Thermal Power Plants (CSP-Plants) have some technical advantages over photovoltaic (PV); Sunlight is concentrated to create heat, which may be used directly to generate steam and drive a turbine, or it may be stored cheaply and efficiently. Steam can then be generated at night from stored heat, and CSP plants can generate power also at night or when clouds are passing through. Gas or bio-fuels may be used as a stop-gap source of heat when there is not enough sun on cloudy days. These things mean that CSP plants can normally deliver power on demand whenever it is required.

Creating a political framework is very simple: in the Sunbelt countries and in client countries, changes are needed in government policies and in the relevant laws and regulations to create a favourable commercial environment for DESERTEC developments.

Creating that favourable commercial environment is relatively easy in countries like Australia, China, India and the USA, where there is only one government involved, and it is harder to achieve when different countries have to co-operate (as in the EU and nearby sunbelt countries). However, with the right political will, these problems are soluble everywhere. It is in everyone's interests that political leaders throughout the world take the necessary steps to facilitate DESERTEC developments.

The technology is ready to go, and investors are interested. What are we waiting for?

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Biofuels: Risks and Reward

Joao de S.B. Paes de Carvalho

Summary

This paper's objective is to present the opportunities and the constraints that have to be overcome to change the energy matrix to an environmental friendly mode. We will discuss renewable energies, with an emphasis on those that have a strong biotech input: ethanol, biodiesel and biogas and also present a brief description of our algae project. As with changing any system with so many vested interests, the substitution to cleaner energy technologies will be slow and will face strong resistance. To overcome that, cleaner energies will have to become cost competitive, the tax systems will have to provide incentives and there will need to be support from consumers.

Introduction

Humanity has always searched for an eternal source of energy. That search has proved to be elusive and the best approach to it has been the use of power derived from nature. Today, due to several environmental menaces we are facing, humanity is looking to change the 20th century pattern of energy consumption, which was based on fossil material. The substitution of coal and oil is not an easy task due to the sheer size of the volumes employed. It will take many decades before we can reach a balanced energy production/consumption model that will not harm the environment to the extent that it is being done now.

Figure 1. The Elusive Dream: The Continous Engine

We must understand that there is no completely clean form of energy. All energy sources have an environmental foot print, small or large. Production, transportation, delivery to consumers and consumption will always leave its mark on the environment. Unfortunately, humanity has used harmful fossil material, coal and oil, to a much larger extent and at faster rate that it should have and that is proving to be disastrous for mankind and the environment. There has been an overproduction of GHG that will have a lasting impact on world climate.

And, not the least, we have become voracious in terms of energy consumption. There is no way that in future US and, to a lesser extent, European and Japanese standards of per capita energy consumption can be transferred to the rest of the world. We will have to restrict energy usage and use it more efficiently.

Where we want to go and the obstacles to overcome

I think that, in environmental terms, we must arrive at a low carbon consumption society. With the present levels of emissions of GHG, the heating-up the Earth is unavoidable, as is the disruption of agricultural production. The increased occurrence of natural disasters are also a certainty. Worst of all, they will be more severe, as always, for the poorer countries that do not have the technologies nor the resources of richer nations.

We also must have a diversified and decentralized energy production matrix as the large investments for energy transportation, be it power lines or pipelines, are deleterious for the environment and cannot reach the people of many less developed regions were the economies of scale do not provide a return for those investments. Thus, smaller production units and diversified forms of energy are more adequate for many regions not served today by appropriate supply and will become more prevalent in areas were the new energy industries are developed and deployed.

Another preoccupation is that the new energies must be sustainable, economically and environmentally, ie, they have to be competitive and have a small environmental footprint.

In the competitiveness field, we have to overcome the government subsidies and tax breaks, like the ones US government grants to coal and oil industry, plus the fact that those polluting energy sources do not pay for its environmental footprint, distorting the pricing system to their favour.

Other factors that must be overcome are the resistance to change; the relocation of labour between traditional and new industries; reducing negative impacts on established industries like oil, gas, coal, automotive and transportation; possible negative impacts on government finances (it is a lot easier to collect taxes from large, centralized industry); and, last but not least, people's habits.

Cleaner energies

When it comes to clean energy technologies, the choice is potentially extensive.

wind	waves	Geothermal
solar	photovoltaic	Magnetic
hydroelectric	nuclear	fuel cells
ethanol	biodiesel	Biogas

Each has its own potential and some are quite developed already, some are being deployed and some are in

This paper will address three biotech-based technologies: ethanol; biodiesel and biogas.

Looking at table 1, there is no doubting that 'traditional' gasoline—diesel and natural gas—packs more power per unit of weight and volume and produces more power per unit of CO_2 kg, except for methane. This suggests that biofuels have some way to go to compete with traditional fuels.

The main challenges are:

- For ethanol and biogas:
  - Improve microbial and operational efficiency of the systems

- For biodiesel:
  - Develop efficient crops for production, improve the production technology

FUEL		MJ/kg MJ/L	MJ/CO^2 kg				
Ethanol		25		20		13	
Gasoline		42		30		15	
Biodiesel		38		35		13	
Diesel			48		40		14
Methane (biogas)	55		23		20		
Nat. Gas		44		27		15	

Cleaner biofuels

Ethanol

Sugar cane today is the crop of choice to produce ethanol, but it can be produced from several other such as corn as well as sorghum, beets and other plants. Cellulose is another source for ethanol.

As the data below show, cane-based ethanol produces more liters per hectare compared with ethanol from corn and also has a smaller carbon footprint

Sugar Cane vs Corn Ethanol

	CANE	CORN
Litres/Hectare	7.000	4.000
GHG emissions reduction	90%	30%
Carbon/MJ energy (grams)	73	105

The opportunities for new technical and scientific developments in sugar cane ethanol production will be centered on the following areas:

- Improved cultivars with disease resistance, higher sugar content, lower water requirements
- Better cultivation methods with more mechanization, soil conservation, nutrient absorption
- Better enzymes with higher resistance to ethanol concentration and heat

For cellulosic ethanol the improvements will come from R&D in:

- Enzymes, yeast and bacteria research (5 carbon)

- Lignin and hemicellulose breakers
- Cultivars with more cellulose and less lignin

Biodiesel

As ethanol, biodiesel can use several raw materials for its production:

- Vegetable oils
- Animal fat
- Waste water fat
- Microorganisms oil

The main areas for biodiesel R&D are centered on:

- Non-edible cultivars
- Bacteria and enzyme
- Production processes
- Algae oil

Biogas

Knowledge of gas from waste products dates back to ancient Persian civilization. In the last millennium, Marco Polo refers to its existence in China; in 1630, Johannes Baptista Von Helmont conduct research and in 1859 the first sewage plant to use bio-digestion was built in Bombay, India; and later in 1895, the streets of Exeter, England, were lit up using biogas.

Biogas can use:

- Industrial residues
- Food industry wastes
- Municipal wastes
- Sewage
- 'Energy' crops

The use of biogas is increasing for a number of reasons:

1. Fuel costs have been rising steadily, making its production competitive for use in cooking and heating, mainly in poorer areas with scarce wood supply.
2. It has simple design and low installation costs.
3. Production is possible in small sites, reducing the cost to supply energy to rural areas.
4. Improvements in the technology and an emphasis in the use of renewable energy sources.
5. The gas produced, mainly methane, is one of the major causes of the greenhouse effect, and large, open air, municipal waste dumps are an important producer.

Many municipal dump sites are now prepared to recover the methane and use it for heating and energy instead of letting it go to the atmosphere.

6. To improve biogas production process and energy recovery, R&D is required for:

   – Pre-treatment of fermentable biomass by heat/pressure
   – Reactors design and feeding strategies
   – Enzymes and bacteria
   – Energy crops

Our Project – Algae Oil

We are presently working on a project to produce oil, carbohydrates and protein from algae.

The basic parameters for this project are:

- Industrial waste feedstock
- Open ponds
- Oil and protein objective

There are many projects competing for what I could call the Holy Grail of inexhaustible and inexpensive fuel systems. Some are funded with a lot of money; some are done by R&D institutes, some by corporations. There was a large effort made by the U.S. Department of Energy's, Office of Fuels Development, that funded the Aquatic Species Program from 1978 to 1996, and that established the basic knowledge for those groups that are now reviving the theme.

Still, there are relatively few successes and it seems that the volume production of oil derived from algae will take some time to materialize. Yet inspite of these difficulties, we decided to fund an effort to develop breeding and extracting technologies, as we have access to large quantities of the industrial residue chosen.

So what are the main problems to overcome? They include: algae strains resistant to open ponds invaders; high oil and protein yield algae strains; nutrients and CO_2 absorption and a need for more efficient photosynthesis.

Opportunities and risks

As I have described, there are myriad opportunities for cleaner energies in the fuels that I have described. There are also risks and constraints that have to be resolved before biofuels will join the mainstream.

The International Energy Agency expects that biofuels will quadruplicate in the next 20 years and they are expected account for about 10% of world demand. The US Energy Policy Act (2005) aims at replacing 30% of transportation fuels by biofuels. The European Union aims at 10% use of biofuels up by 2020.

What will benefit biofuel uptake is that oil prices will rise on the long run; that technology is reducing the cost advantage of fossil fuels; and a need to reduce GHG emissions is another driver.

But the risks of biofuels include: they use very large quantities of water; they are likely to add to deforestation and therefore biodiversity loss. Biofuels production on an industrial scale will need fertilizers and pesticides leading to further pollution and in the long run land degradation and soil erosion. Furthermore, while biofuels remain lucrative for farmers, it is likely that they will be grown at the expense of food crops.

Conclusion

There can be no change without pain. Change from established models is not easy, fast, resistance-free nor secure.

We believe that, in the long run, with the opportunities provided by new technologies and solutions to the risks outlined previously, the world will see a paradigm change in the way we produce and consume energy. We are already seeing many advances in that area.

Four points are fundamental in concluding:

- R&D is needed to make cleaner energies cost competitive and that will need government incentives, as well as investors and corporations willing to take risks
- The large players—the oil and vehicles industry—will have to join because they have the marketing and distribution might that can bring biofuels to every corner of the globe
- Governments have to build tax system that will provide incentives and not disincentives
- Consumers must give support.

But I am optimistic that we will get there. Cleaner energies will become mainstream and will substitute in the next 20–50 years most of the fossil fuels derived energy required for our lives.

9

INTRODUCING

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The BA Science Supercourse

Noha Adly, Najeeb Al-Shorbaji, Jesse Huang, Ronald LaPorte, Faina Linkov, Magdy Nagi, Gilbert S. Omenn, Nicholas Padilla, Francois Sauer, Ismail Serageldin, Eugene Shubnikov

Summary

The Global Health Network Supercourse project is a library of online lectures on public health and medicine that originated at the University of Pittsburgh WHO Collaborating Centre for Disease Monitoring and Telecommunications in late 1990's. The parent Supercourse site at the University of Pittsburgh currently has over 46,000 registered faculty members and scientists from 174 countries and a library of over 4541 high quality educational lectures. Science Supercourse is a sister project to the Supercourse, designed to go beyond the topics of health and medicine and reach out to other areas of science, coordinated from the Library of Alexandria in Egypt. BiovisionAlexandria2010 had a round table discussion where coordinators of the Supercourse projects from various countries around the world had a chance to discuss their ideas about the future development of this truly global effort.

Introduction

The Global Health Network Supercourse project is a library of online lectures on public health and medicine that originated at the University of Pittsburgh WHO Collaborating Centre for Disease Monitoring and Telecommunications in late 1990's. The parent Supercourse site at the

University of Pittsburgh currently has over 46,000 registered faculty members and scientists from 174 countries and a library of 4541 high quality educational lectures in 31 languages. As of August 2010, Supercourse had 698 translated or original lectures in Spanish, 470 in Chinese, 227 in Russian, representing three major Supercourse initiatives that will be discussed in this paper. Supercourse of Science is a sister project to the Supercourse, designed to go beyond the topics of health and medicine and reach out to other areas of science, coordinated from Bibliotheca Alexandrina in Egypt.

The Supercourse of Science was launched at Bibliotheca Alexandrina in Egypt in January 2009, under the leadership of Dr. Ismail Serageldin, the director of the Library. In April 2010, the program rolled out the beta version of its new online system, adding more search features and more lectures than the parent library. Science Supercourse is a project designed to capture and share educational lectures about various scientific areas in an open source library. Science Supercourse system currently has over 100,000 educational modules, obtained from crawling the Internet. While the original foci of the Science Supercourse are Global Health, Agriculture, Environmental Science, and Computer Engineering, the plan is to extend to other scientific and engineering areas in the next several years. Each area will have a 'community of practice' to stimulate contribution of high-quality lectures and provide guidance and review on coverage of the fields. Bibliotheca Alexandrina, along with the developers from the University of Pittsburgh, will lead on coordinating this project with financial support from the Swiss Development Corporation.

Bibliotheca Alexandrina is the most logical place to host the Science Supercourse. The Ancient Bibliotheca of Alexandria was the greatest library of the ancient world. Named after Alexander the Great, it flourished under the patronage of the Ptolemaic dynasty and functioned as a major center of scholarship from its construction in the third century B.C. through 48 B.C. Similarly, the Supercourse has been designed as a central repository of knowledge in the format of PowerPoint lectures. When the Bibliotheca of Alexandria was burned, the unique content of its encoded explicit knowledge was destroyed. We are hoping that the Supercourse can save our scientific lectures from destruction by recycling them in a universal easy-to-access repository, with multiple backups on local servers around the world. In the Supercourse, we believe that the educator plays a pivotal role in the education process. Thus, both the parent Supercourse and the new Science Supercourse are designed to empower the educator. In this new age the role of the Educator is expanding to become a catalyst for the student's mind, fostering independent thinking and innovation. The Supercourse project has several key directions of work that will be discussed in the next several sections.

Former Soviet Union (FSU)/Russian Language Supercourse

FSU/Russian Supercourse project started in 2000, when it became clear that Russia and FSU countries need an inexpensive but effective approach to disease prevention and health promotion, which will improve the system of Public Health information sharing. The Internet coupled with prevention promises to be the answer, as much of Public Health is information transfer. The Russian/FSU Internet Prevention (I-prevention) program, coordinated by Dr. Eugene Shubnikov, consists of the following key elements:

- Network of the scientists involved in prevention and the Internet in Russia and FSU
- Russian Language or Russia/FSU's connected Public Health Library of 227 lectures on the Internet
- Scientific cooperation between Russian, FSU, US and scientists from around the world in the field of Epidemiology, Public Health and Internet

The former Soviet Union (FSU) Internet prevention group consists of about 1000 members from all the 12 Newly Independent States (NIS) and Baltic countries, as well as Russian-speaking professionals around the world.

Latin-American Supercourse on Epidemiology, Internet and Global Health

Health professionals from Mexico and Latin-American countries had limited access to continuing education because of the high cost. Dr. Nicholas Padilla and his team joined forces with the Supercourse (SC) team to develop the Latin-American Supercourse (LASC) in Spanish containing nearly 700 lectures. In two years, we had almost 30,000 hits to the Latin American Supercourse pages and collected over 4000 evaluations of lectures. Also, Latin American Supercourse lectures or lectures translated into Spanish rapidly obtained high Google Page rankings, in almost all categories of LASC.

One objective of LASC is to produce Just-In-Time lectures. Just in time lectures refers to educational modules created just in time to share knowledge on a global event that affects health (disasters, epidemic or pandemic diseases, etc). The goal of JIT knowledge is to treat the "fear epidemiology", that comes into being when the general public does not understand and fears events such as Influenza A(H_1N_1) (Swine Flu) (March 2009). When the first case was diagnosed in Mexico, the Supercourse team in Celaya alerted the Supercourse team in Pittsburgh to launch a much-needed lecture on this issue. In April 2009, Rashid A. Chotani and the Supercourse team launched the first version of this lecture in English, Russian and Spanish; the lecture was updated daily for 10 days and then monthly with the course of pandemic influenza in the world. The 15th version of this lecture has been translated into 14 languages. We obtained rates of access to this webpage which were ten times higher than for regular lectures. This lecture was a communication channel between health professionals in Latin-American, North American, European and Asian countries. This lecture has been used in some Latin-American countries as an educational material for health professionals and the general population.

Chinese Supercourse

Professor Jesse Huang launched the Chinese Supercourse, containing 470 lectures. He encouraged medical students in Beijing to translate Supercourse lectures into Chinese mandarin. In addition to the online lectures, Chinese colleagues pointed out that we could work on a much larger scale. Specifically, Dr. Huang presented the Supercourse on Chinese TV (CCTV), thus exposing the Supercourse to 500 million viewers. The H_1N_1 lecture also had great impact on Chinese media. The Supercourse has been reported by a prestigious magazine Liaowan (with impact similar to Newsweek). Reports have been suggesting that Chinese CDC representatives downloaded the PowerPoint of this lecture and have used it for training.

Collaboration with WHO

In the past several years, the Supercourse project has been collaborating with the WHO, especially in the area of distribution of Supercourse DVDs to medical school libraries. The World Health Organization is the United Nations specialized agency for health. It was established on 7 April 1948. WHO's objective, as set out in its Constitution, is the attainment by all peoples of the highest possible level of health. With the help of Dr. Najeeb Al-Shorbaji from WHO, Supercourse team effectively distributed Supercourse DVDs to all accredited medical schools around the world. This effort was very important, as most medical schools provide little training on global health and disease prevention. By having access to the Supercourse lectures, world's medical schools are better equipped to teach about these important areas. WHO is very active in the field of global health education. Two efforts described below, WHO Global Health Library and WHO Knowledge Networks are good examples of such areas of collaboration.

WHO Knowledge Networks (based on WHO website)

The WHO Regional Committee for Africa at its fifty-sixth Session in 2006, adopted strategic directions and a related resolution on Knowledge Management (KM). The strategic directions seek 'to contribute to the improvement of health system performance and outcomes through effective KM in health'. The resolution recognizes that KM is all about providing the right knowledge for the right people (policy-makers, practitioners, health systems managers and the general public) and in the right format in order to strengthen health systems and improve health outcomes.

The following 'Knowledge Networks' contribute to WHO's efforts to improve access to the world's health information and to share and reapply experiential knowledge:

- AFRO Library Services
- Headquarters Library & Information Networks for Knowledge
- Health InterNetwork Access to Research Initiative (HINARI)
- The Global Health Library
- Africa Health Workforce Observatory
- WHO Collaborating Centres

WHO Global Health Library (based on WHO website)

The objective of the Global Health Library (GHL) is to contribute to radically increase access to information and scientific evidence on health, particularly in developing regions. GHL is promoted and led by WHO as part of its strategy of knowledge management in global public health. The GHL aims to 'strengthen, promote and develop worldwide networks on the collection, organization, dissemination and universal access to reliable health sciences information'.Based on existing initiatives, virtual libraries, networks, systems, products and services and to increase their interoperability, visibility and accessibility, the main objective of the GHL proposal is to maximize cooperative activities in networks and minimize duplications. The GHL is designed to create the global space that will promote and progressively connect local, national, regional and international flows of information on health. The GHL was publicly launched in September 2005, during the 9th World Congress on Health Information and Libraries (ICML9) and the 7th Regional Congress on Health Sciences Information (CRICS7), held in Salvador, Bahia, Brazil.

Science Utilization: Report from Google Analytics

While anecdotal evidence suggests that the Supercourse project is much loved and has great impact all over the world, we looked at Google Analytics to see how many access the Supercourse site. We added Google Analytics codes for index files to all Supercourse lectures on January 15, 2009. We have estimates for Google Analytics statistics for the period of August 1, 2009, to August 1, 2010. During the past year index files or front pages of lectures got 240,511 unique visits; thus, on average, Supercourse lectures had 20,042 visits per month or 657 visits per day by users from 211 countries/territories. The top ten countries were United States, India, UK, Canada, Australia, Philippines, Malaysia, Pakistan, Mexico, and Egypt. Google estimated that these visitors were speakers of 119 languages, with the top languages being English and Spanish.

These Google Analytics statistics show the global impact of Supercourse Lectures. Additionally, they demonstrated that the Supercourse has large numbers of 'loyal' users who use Supercourse frequently. Google Analytics has 'loyalty' statistics which estimate the number of new and returned visitors of the Supercourse main page. During past year 81.5% of the visitors of Supercourse lectures were new. In the same period we had 437 visitors who visited the Supercourse lectures more than 200 times. We never would have expected this high degree of traffic. One of our future directions is to do more formal research on Supercourse 'traffic'.

Global Health: Can the Science Supercourse Raise Interest in this Important Area?

In our mind, the Supercourse project could stimulate the public's interest in global health. Google Trends (www.google.com/trends) is a tool that measures the number of searches on specific topics in the Google search engine. It is a direct measure of 'Interest' on the web. Figure 1 below demonstrates searches on the term 'Global Health' in the past 6 years. Interest has been relatively stable, spiking up around the times when news media shared information about Bill Gates donating money to Global Health causes or the general

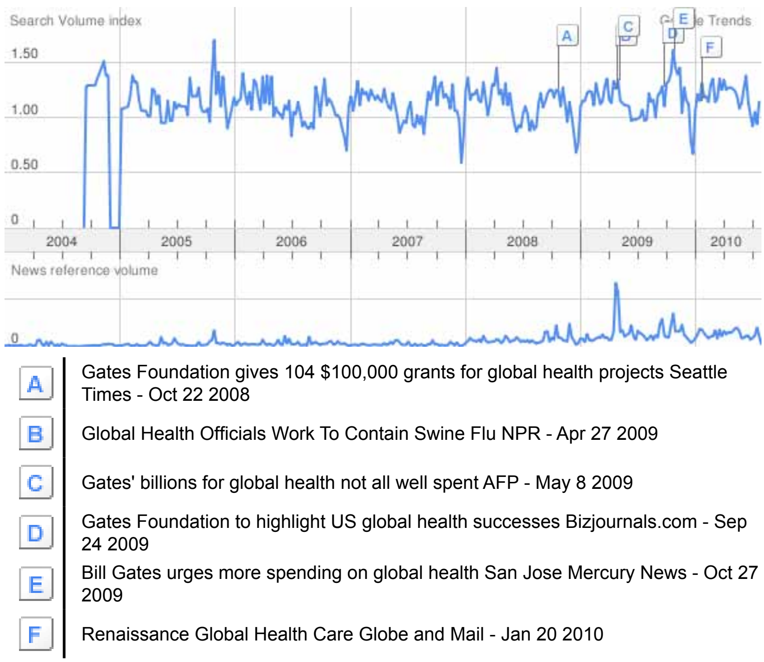

Figure 1. Google Trend search for the term "Global Health" for the period of 2004-2010. (assessed July 2010).

media covered the swine flu. It is our hope that the Supercourse of Science and the parent Global Health Network Supercourse project together will be able to spike Internet Users' interest in both in global health issues and in broader areas of science and technology.

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Egyptian Young Academy of Science

Nadia El Ansary

EYAS is an outcome of a program supported by the Inter Academy Panel (IAP) on International Issues.

EYAS is virtual academy, affiliated to the mother academy (Academy of Scientific Research and Technology ASRT), aiming at empowering youth (young scientists and juniors) to play a crucial role in developing future strategies for socio-economic development.

EYAS values are stressing on the importance of sustaining communication and productive partnership between EYAS members and civil society institutions concerned with supporting excellence in STI and enhancing their participation in planning the future.

Vision

'Strengthening the role and participation of Youth in outlining science and technology policy'.

Mission

'Support juniors in their development as world class scientists'.

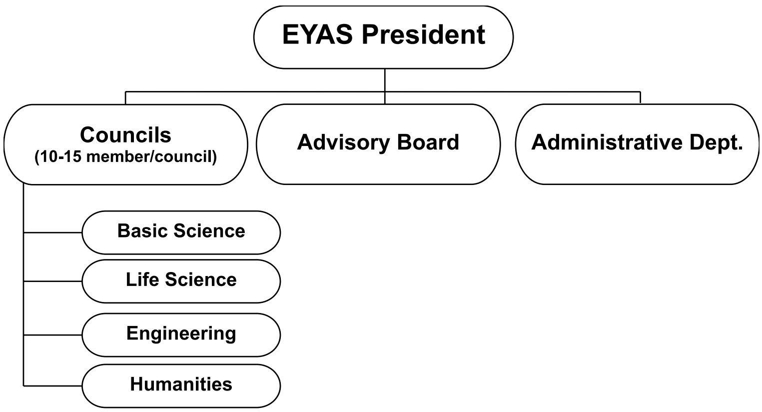
Young Scientists should contribute extensively in knowledge transfer

Objectives

- Increase the interest of juniors in S&T
- Promote juniors' capabilities to compete worldwide in scholarships, grants and prizes
- Prepare future scientists capable to apply state-of-the-art techniques to lead STI in their organizations
- Linking the scientific community with the activities of the private sector and the civil society

EYAS Organization

EYAS consists of four panels (councils) will be formed, each including 10 to 15 scientists who come from Egyptian universities and research institutes and working in different fields, including: Basic Science, Engineering, Life Sciences and Humanities.



Memberships

- Acting members (4 councils members, PhD holders, elected every 3 years, Egyptians studied abroad should be represented, age limit 35–40)
- Affiliated members (undergraduate students 'schools, universities', researchers, all youth, age limit up to 40)

- Advisory board (Elders council: ASRT president + EYAS president + member of Egyptian committee of ETHICS + scientific community ICONS + 4 representatives of EYAS councils elected annually by each council)
- Follow-up committee (EYAS members + representatives from the public and private sectors and NGO's to work out a suitable mechanism of communication with the youth sector)

Members' selection criteria

- Age: up to 40 years (this condition not valid for Advisory board and Follow-up committee)
- Demonstrating excellent research accomplishments
- Experience in education and/or scientific administration
- Display leadership qualities
- Have excellent communication skills and fluent in English
- Interesting in science policy and science communication
- Familiar with global issues and international programs in S&T and science-based sustainable development

Success Story

Scientists for Next Generation (SNG)

Academy of Scientific Research and Technology (ASRT) offers grants for a new generation of graduates to a master's degree, in order to bridge the gap between scientific research and the requirements of the national labor market, which requires a high degree of skill in the performance, to get good opportunities for cooperation with leading scientists and participate in research projects in scientific fields of national interest.

'SNG scholars will be the main core of EYAS'.

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Fifty Years of Academic Cooperation Between Germany and Egypt

Christian Hülshörster

Europe without borders and the globalization of markets are characteristics of growing internationalization. International experience combined with tolerance and openness for other cultures is considered to be key competence of the future. Education enables people to make use of the opportunities of open borders and worldwide communication. Science thrives on exchanges across all borders. However, international collaboration in science is possible only on the basis of internationally agreed cooperation. Implementing these collaborations often depends on the financing of exchange programmes from state funds. International exchanges are very much alive in the German education system, too. They range from programmes for exchanges of pupils at schools to programmes for exchanges in academic education. Young people get to know new cultures and languages in exchange programmes. This is the basis for skills that are necessary in a world that is growing together.

The German Academic Exchange Service (DAAD), acting on behalf of the German government, is creating the possibilities by means of international cooperation. The DAAD's Regional Office in Cairo, celebrating 50 years of successful work in Egypt in 2010, has been working in five major areas:

- Scholarships for foreigners: Supporting future foreign elites at German universities and research institutes
- Scholarships for Germans: Supporting future German leaders in their studies and research abroad

- Internationalisation of German universities: Increasing the international appeal of German universities and promoting the international dimension in German higher education
- Promoting German Studies and the German language abroad
- Educational cooperation with developing countries: Promoting academic, economic, and democratic development in developing and reform countries

Especially since the German – Egyptian Year of Science & Technology in 2007, Germany has been one of the major partners of Egypt's scientific and higher education community. Jointly financed program schemes, like the long-term Ph.D. scholarship program GERLS or the German – Egyptian Research Fund (GERF) are cornerstones of a cooperation build on trust, respect and the belief that scientific success in today's world is to a high extent depending on international team work.

Besides Egypt also other countries of the MENA region showed rising interest in cooperation with Germany in the field of higher education and scientific research:

- New interest in co-financed programs (Master, Ph.D.) – Syria, Egypt, Gulf
- Double and Joint Degrees (Egypt, Syria, Jordan)
- 'University Export' (GUC, GJU, GUTECH, TU Berlin El Gouna – Heliopolis University)
- New focus on research cooperation and industrial application (Egypt – GERF, GESP)
- New interest of important German players in the field of research cooperation (DFG, HGF, MPG, FHG)

Good cooperation in higher education and building trustful relationships needs time. The success story of the German-Egyptian cooperation was built over the last 50 years. It probably can't be reproduced in 5 year's time in the gulf region.

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How PepsiCo Bridges the Agriculture-Nutrition Divide

Carmela Rivero

Summary

PepsiCo is the second largest food company in the world. Its portfolio is composed of beverages and foods-these last ones made all from agricultural sources: Potato, Corn, Wheat, Oats, and Rice. Guided and Inspired to Build a Better Tomorrow, under CEO Indra Nooyi's call "Performance with Purpose", PepsiCo supports farmers around the world by training them to get better yields, more nutritious crops, while respecting biodiversity and elevating the standards of responsible sustainability. To further its reach and impact, Pepsico partners with governments and NGOs such as Embrapa member of Harvest Plus on Biofortification, with the InterAmerican Development Bank to secure sourcing and enable credit for farmers. Dozens of thousands of families benefit from PepsiCo's way of living Corporate Responsibility. Three cases were presented from Mexico, Peru and Brazil. This is the way PepsiCo constributes to a Better Tomorrow through Performance with Purpose.

About PepsiCo

PepsiCo offers the world´s largest portfolio of billion-dollar food and beverage brands that bring joy to our consumers in over 200 countries. PepsiCo now employs approximately 275,000 people who are united by our unique commitment to sustainable growth called Performance with Purpose.

At PepsiCo, Performance with Purpose means delivering sustainable growth by investing in a healthier future for people and our planet. As a Global Food and Beverage Company with brands that stand for quality and are respected household names—Quaker Oats, Tropicana, Gatorade, Lay´s and PepsiCola, to name a few—we continue to build a portfolio of enjoyable and wholesome foods and beverages, find innovative ways to reduce the use of energy, water and packaging, and provide a great workplace for our associates. Additionally, we respect, support and invest in the local communities where we operate, by hiring local people, creating products designed for local tastes and partnering with local farmers, governments and community groups. Because a healthier future for all people and our planet means a more successful future for PepsiCo, its Promise lies in three pillars Human Sustainability, Environmental Sustainability and Talent Sustainability.

PepsiCo's global goals in the area of human sustainability stepping across industry boundaries to address core health and wellness challenges in order to make our products more wholesome and nutritious. Our goals are aggressive and respond directly to changing consumer habits and, what we believe is our inherent responsibility as a global food and beverage company.

Lifestyles, and in turn, consumption habits, are changing around the globe – particularly in markets like China and India where there is a direct correlation between food consumption and rise in GDP. As we see this trend line in emerging markets, research tells us that consumers across the U.S. and Europe want healthier products that are affordable, and, importantly, taste great. Because PepsiCo is committed to responding to market desires—and broader issues like local and international health epidemics—we are ensuring that core PepsiCo products from brands like Lays, Pepsi, Tropicana and Quaker can be part of a balanced, healthy lifestyle for consumers around the world.

Our work in this area is firmly grounded in science, agriculture and technology and we are collaborating with expert organizations like the World Health Organization and the World Heart Federation in order to fulfill these commitments. With these goals guiding our way, PepsiCo will continue to move toward supporting a healthier future for our consumers.

Increased global attention being given to under nutrition

In January 2009, the International Monetary Fund predicted that global economic growth would slow to its lowest rate in sixty years[1]. At the same time, the number of people suffering from severe under nutrition and food insecurity reached 1 billion, most living in developing countries[2]. Concerns about hunger have dominated debates at recent United Nations meetings in Madrid (January 2009) and Rome (June 2008), as well as during the January 2009 World Economic Forum in Davos[3].

During 2008, the results from newly published cohort studies demonstrated that early stunting and micronutrient deficiencies lead to permanent intellectual and developmental outcomes and that there were intimate links between early stunting and the later onset of diabetes and cardiovascular diseases[4]. Research on the importance of diet and nutrient intake has consistently highlighted the need for early childhood education and intervention at both ends of the over/under spectrum[5]. Further, from cohort studies in developed countries, we now have stronger evidence linking early childhood under nutrition and obesity to school performance[6]. As such, the quality and quantity of childhood nutrition has never mattered more[7]. The notion of 'optimal nutrition for all' is emerging as a unifying paradigm for both nutrition science and for corporate actions.

The role of the food industry in addressing global nutrition challenges

The food industry has a vital role to play alongside governments, nongovernmental organizations (NGOs) and academics in addressing nutrition. On May 13, 2008, the CEOs from eight multinational food and non-alcoholic beverage companies and one major national company, with combined annual sales revenues totaling more than $350 billion USD[8] signed a Global Commitment to Action in support of implementing the World Health Organization's Strategy on Diet, Physical Activity[9] and Health. In addition to addressing chronic diseases, the CEOs committed to advance work related to under nutrition.

While the last decade has seen the flourishing of public-private partnerships between pharmaceutical companies and the public sector that has lead to the development of, and access to, essential new drugs and vaccines[10], truly influential private-public partnerships between the food industry and governments have yet to develop.

Changing economic realities leading to new ways of doing business

The economic and financial crisis is stimulating discussion about the future role of business in relation to major social problems like hunger. There is growing acceptance of the need to develop new business models that simultaneously generate financial profits critical for long-term growth while concurrently improving both population health and the environment. PepsiCo CEO Indra Nooyi terms this 'Performance with Purpose,'[11] Bill Gates calls it 'creative capitalism,'[12] and Muhammad Yunus refers to the evolution of 'social business.'[13] This mindset creates the impetus for food companies to address hunger.

Multinational food companies are publicly supporting agencies of the United Nations to reach the Millennium Development Goals (MDGs). The first of these goals focuses on reducing both poverty and hunger in developing countries. Below, we highlight eight actions by food companies that will have a strong impact on addressing MDG. Our comments apply only to food and beverage manufacturers.

Investment in agriculture, especially smallholders

This is crucial to the long-term viability of the world's food supply, as well as to help improve the nutritional status of the very poorest individuals[14]. Business could strengthen food value chains by providing higher quality seed and micro-credit to farmers, improving the affordability of fertilizer and efficiency of irrigation systems and shifting to rely more on local sourcing of foods.[15] The World Economic Forum recently highlighted successes underway in this field, like General Mills' actions in support of local high-value corn in China as opposed to imported products. PepsiCo's work with local potato farmers in Peru, Mexico, Brazil, China and South Africa; with citrus farmers in Indian Punjab; with corn farmers in rural Mexico and oats farmers worldwide are examples of this approach. Importantly, action aimed at the poorest billion will be led by governments, using new funding mechanisms, but should be complimented by corporate philanthropy. Examples include Unilever's multi-year, monetary commitment to the WFP (World Food Progamme) to help combat child hunger in Kenya, Indonesia, Ghana and Colombia, and the PepsiCo Foundation's grant to Save the Children in India and Bangladesh that will ensure that up to

50,000 people obtain food, deworming drugs, breastfeeding advice and the tools for proper hygiene.

Agriculture must deliver more food, but also the best possible nutrition. Indra Nooyi at the 2009 World Food Program stated: 'How do we make sure that agriculture is organized to serve the nutrition needs of the world?' Agriculture focuses on the quantity of food produced and its price, Nutrition focuses on the quality of the food and who it is getting to.

Agriculture is a key component along the PepsiCo value chain. Therefore we have developed several programs to support agro from an environmental and social scope, operating under a Global Sustainable Agriculture Policy, and as a Signee of UN Water Mandate.

PepsiCo's farming expertise allows us to transfer nutrition science, irrigation techniques and development of crops to small farmers always in the most responsible ways possible.

One Example is Lay's Andinas, A Socially Responsible Product, Designed To Help Out Native Peruvian Farmers To Improve Their Living Standards. Lay's Andinas benefit more than six thousand potato farmers

Growers are offered training, including farming technical assistance. With this product PepsiCo Foods Peru is: Investing to develop educational programs for the Andean communities, Contributing with technical support to boost potato yields thus improving families income per farm.

PepsiCo Chairman and CEO Indra Nooyi visited PepsiCo operations in Santiago, Chile and Lima, Peru this week to drive the company's Performance with Purpose message forward in these countries with several key announcements.

In Peru, she announced the creation of PepsiCo's Agricultural Development Center (CEDAP) – a $3 million investment over the next three years that will focus on the development of new varieties of potatoes and other tubers and roots. Indra met with Peru's President, Alan García, to discuss the project. The Center, which is the first of its kind in Latin America, will house research on the current Peruvian varieties of roots and tubers with an ultimate goal of developing new varieties that can be used to improve the company's product portfolio. The knowledge and experience gained will be shared with other PepsiCo businesses around the world, especially those in tropical and subtropical zones similar to Peru.

The Center will focus on researching the current Peruvian varieties of roots and tubers with an ultimate goal of developing new varieties that can

be used to improve the company's product portfolio. The CEDAP will also create programs of research on other roots and tubers, to develop new and healthier products and to encourage commercial cultivation of these species in ways that preserve biodiversity.

Moreover, the 300 Peruvian potato farmers from throughout the country who supply PepsiCo will also enjoy the benefits of the CEDAP. For these farmers, the CEDAP will be a center of innovative technical support to: optimize resource use and increase agricultural production; improve plant performance and nutritional quality; maintain soil fertility, water and air quality, and biodiversity in agricultural activities; and empower rural communities. The goal is to improve not only the quality of the harvest, but above all, the well-being and quality of life in the areas of production.

A second example is PepsiCo Mexico, who has supported Agriculture Sustainability with the following:

g. Contribution to the Mexican economy by buying 240 000 tons of potato (22% of national crops), 100 000 tons of corn, 30% of total consumption of soft wheat, while supporting Mexican farmers by providing them: Technical assistance; Contract-based schemes, that assure buying the crop; Outreach initiative to educate farmers about sustainable agricultural practices in fields: Campo Limpio program
h. Educampo, a program lead by Sabritas (Mexico PepsiCo Subsidiary) and Fundar Educampo engaged in educating farmers and their families with more than 30,000 hours of training and follow up, indirectly generating new jobs from clean field and media classrooms with benefits to 200 students in

the community. This program contributes to the development of small and medium size low income corn producers close to our manufacturing plants, increasing corn crops productivity, while establishing a long term relationship in contracted Agro (impacting 297 corn producers, attained 165% yield and income improvement and reached 1,485 indirect beneficiaries).

A Third example is PepsiCo Brazil, where in partnership with Embrapa, member of Harvest Plus and AgroSalud, bridges Agriculture and Nutrition. PepsiCo will naturally enhance its products with relevant nutritious ingredients by breeding crops to improve nutrition: Roots, Tubers, Cereals & Legumes via Natural fortification with: Zinc, Iron, Betacarotene. The plan is to leverage Embrapa's Biofortified Cultivar development, and support developing Farmers, contribute on quality, safety and innovation management along the agri-food chain and socio economic impacts to increase value to the bionutritious crops, employ technology transformation and application, collaborate with Embrapa with product prototypes to conduct nutrition valorization and finally implement the new naturally more nutritious crops in our products. Finally demonstrate that through a multi-stakeholder approach we benefit the communities in which we operate giving life to our call Performance with Purpose.

This is How PepsiCo Bridges The Agriculture-Nutrition Divide Through Science and Product Development"

Other Bridges between Agriculture and Industry are:

1. Expanded use of corporations' core capabilities in distribution and quality control
2. Sustained and greater support for fortification of staples and commonly consumed nutritious foods and beverages
3. Innovation and expansion of the portfolio of foods currently available for complementary feeding in settings of acute and chronic under nutrition
4. Co-creation of new and innovative social business models to help combat the global burden of under nutrition
5. Investment in the development of nutrition science capacity, especially in developing nations
6. Innovation of product reformulation aimed at developing low-cost nutritious foods for all markets.
7. Committed advocacy by multinational food and beverage corporations for nutrition-friendly trade policies

Conclusions

In Harvard Business Review, Moss noted that:

When giants transform themselves from impersonal machines into human communities, they gain the ability to transform the world around them in very positive ways… Values turn out to be the key ingredient in the most vibrant and successful multinational (corporations)"

Many major food and beverage companies support this view and are deeply engaged in addressing many aspects of the hunger crises, even as they struggle to define their contribution to reducing obesity. If we are to ever successfully combat global under nutrition, efforts must be sustained by multiple stakeholders from various sectors. We believe that trust is built through industry's demonstration of practical actions that improve health, and recognition of these actions by governments and NGOs. Only through new and innovative public-private sector partnerships can we truly make a difference.

This is How PepsiCo Bridges The Agriculture-Nutrition Divide Through Science and Product Development.

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Qatar Foundation: An innovative Model for Research and Education

Abdelali Haoudi

Summary

Qatar is taking a novel and pragmatic approach to its future by investing its petrodollars in young people. Through Qatar Foundation (QF), a non-profit organization, Qatar is equipping a new generation of Qataris with the skills they need to transform the economy and take the small Middle East country into a sustainable post-carbon future.

QF uses innovative strategies and programs focusing on capacity building and character development to lay the groundwork for a sustainable future. Its flagship project, Education City (EC), is fast establishing itself as a regional educational hub. With over 85 member organizations, EC is being touted internationally as an intelligent and effective tool for carefully-planned development. Its graduates will go on to transform their communities and their countries, as well as their lives.

At the heart of EC are six hand-picked universities, the branch campuses of prestigious international institutions that are delivering some of their most renowned programs. These institutions, combined with state-of-the-art facilities, make Qatar a pioneer in education in the Middle East. The longer-term objective is to ally world-class education with research that will give birth to scientific breakthroughs, projects and partnerships that will benefit not only Qatar, but the world.

Therefore, in the last five years, a new impetus was given to supporting and expanding research in EC by launching new centers as purpose to complement the research activities taking place in the branch campuses of the EC.

In this paper I will try to describe how eventually QF—which is investing multi-billions in infrastructure, capital projects and facilities—seeks to have more than 2000 faculty, researchers and staff working at every level of the education-research continuum allowing it to become The Silicon Valley of the Middle East.

Introduction

Eleven centuries ago, an Islamic renaissance occurred in Baghdad, attracting the best scholars throughout the Muslim world. For the next five hundred years, while Europe was mired in the Dark Ages, the Arabic world was in the forefront of science – in sad contrast to the state of the majority of the Arabic countries today.

Arab countries missed the industrial age and continued to import most needed machinery and products from others. Similarly, they missed the nuclear age and did not contribute to unlocking the secrets of the atom or the peaceful uses of radiation. The space age also passed with little notice in the Arab region. It behaved as a spectator of a sport who does not know the rules of the game.

Today, we live in the information age and Arab countries have a great chance to contribute due to the wise vision of the leadership in Qatar.

To achieve a sustainable future after its oil and gas reserves run out, a 2007 study of Qatar's readiness to become a knowledge economy, led by the state Planning Council, identified, amongst others, a skills gap in the labor market. The government's wise response was a framework document —Qatar National Vision 2030—which is now the country's guide to a four-fold development strategy, including the development of human capital. The economic reform efforts are being led by QF and its flagship project, Education City, which is fast becoming a hub of educational excellence in the region.

Established in 1995 by His Highness Sheikh Hamad Bin Khalifa Al-Thani, the Emir of the state of Qatar, and steered by H.H. Sheikha Mozah Bint Nasser Al-Missned, QF is a unique educational experiment and the engine for social and economic change. In line with Qatar's national vision, its initiatives in the areas of education, science and research and community development will help to turn Qatar into a diversified, knowledge based economy by 2030.

Knowledge economies are built on education, innovation, information technology and economic incentives and based on a well-educated and highly-skilled workforce. That is why developing the human capital necessary for Qatar's transformation is founded on fostering a research culture—an environment that encourages the pursuit of new knowledge and the advancement of scientific research. Out of this culture of innovation and entrepreneurship, Qatar plans to drive new technologies into the market. It is backing its vision with investing 2.8% of the country's annual GDP in science and research. Worth to mention that this figure place Qatar in the top ten highest investment in the world and the highest in the Arab world.

Education

What began in 1995 as a high-quality K-12 school for Qatari nationals and expatriate residents has grown into an organization that educates 3,000 elementary, secondary, undergraduate and graduate students from more than 70 countries – and is home to the R&D labs of some of the world's leading multinational firms.

Six world-renowned U.S. universities already operate branch campuses in Education City, offering degrees that do not even mention that the study took place in Qatar – such is the confidence that students receive an identical education and diploma to that from their mother institutions. So far, Qatar Foundation has partnered with Virginia Commonwealth University in design arts; Weill Cornell Medical College in medicine; Texas A&M University in engineering; Carnegie Mellon in business administration, computer science and information systems; Georgetown University in foreign service, and Northwestern University in journalism and communications. QF's Faculty of Islamic Studies offers unique graduate programs in contemporary Islamic jurisprudence, public policy and finance.

But building a beautiful campus and developing and attracting top educators is only part of the goal, according to His Highness the Emir Sheikh Hamad bin Khalifa Al-Thani, The longer-term objective is to ally world-class education with research that will give birth to scientific breakthroughs, projects and partnerships that will benefit not only Qatar, but the world.

Research

Many different approaches can be taken for building a national research program. QF has made three key strategic decisions that fundamentally shape its choice and scope of activities. Those decisions are: to focus on certain fields of science; to support both basic and applied research; and to integrate local and international partners to accelerate the transfer of knowledge.

Scientific Focus

Qatar is a small country, and to be internationally competitive it must concentrate its research efforts in certain areas. Therefore QF has selected three key fields, based on the needs and strengths of Qatar's economy and society:

- Health sciences. Physical and psychological health is fundamental to the quality of life of every person, and Qatar has placed it at the forefront of its development goals for 2030. Further, Arab populations face unique health challenges such as a high rate of diabetes that have not been sufficiently addressed. QF has already established Weill Cornell Medical College in Qatar and is now building the Sidra Medical and Research Center and assembling a biomedical research institute.
- Energy & environment. Qatar has been blessed with the world's third largest reserves of natural gas, which has propelled national wealth and development. Yet an economy overly dependent on petroleum income can be hurt by severe fluctuations in prices, and climate change and environmental protection demand attention. Six oil companies, including Qatar Petroleum, have established R&D centers at Qatar Science & Technology Park, and Texas A&M University at Qatar is focusing on energy and environmental research. They will be augmented by a dedicated research institute being developed by QF.
- Information & communication technology. Digital technologies have become an integral part of everyday life and a driver of entrepreneurship and economic growth. Qatar is quickly adopting these technologies but much opportunity remains to adapt them to the Arab language and develop new applications to serve regional markets. Complementing Carnegie Mellon University in Qatar's computer science and information systems courses, QF is now establishing an IT and computing research institute.

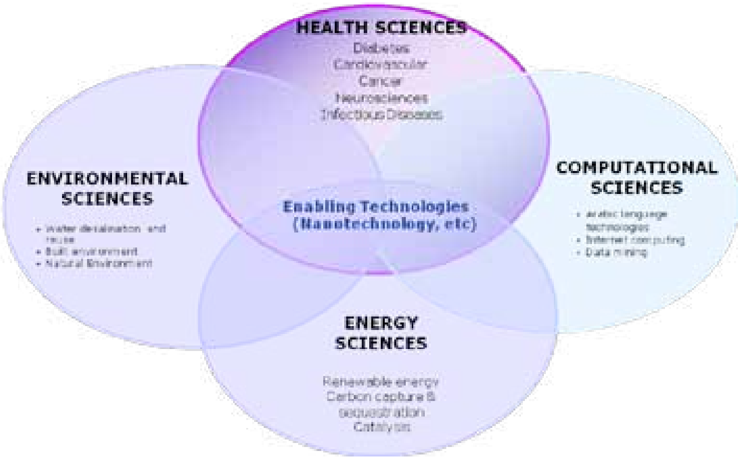

Figure 1. QF Scientific and Technical Research Focus Areas

While these three fields are the focus of Qatar Foundation's research efforts, they will be complemented by initiatives in other technologies. For example the Research Division is establishing a research program in nanotechnology because it is an 'enabling' technology that can be applied to biomedicine, energy and environment. (Figure 1)

Fundamental and Applied Research

Qatar Foundation promotes research from the fundamental, or inquisitive, stage through to development of real-world products. Confinement to fundamental research would miss the benefits being transferred to society, and focusing solely on technology commercialization would fail to achieve Qatar's ambition to be an originator of scientific knowledge.

The Research Division further bases its investment in fundamental research on the observation that technology transfer by itself has failed to convey scientific knowledge, or the capacity to innovate, to Qatar over previous decades. There is no substitute for advanced education and the practice of basic science to build a national research capacity.

Qatar Foundation promotes the full chain of research and development through the following strategy: (Figure 2)

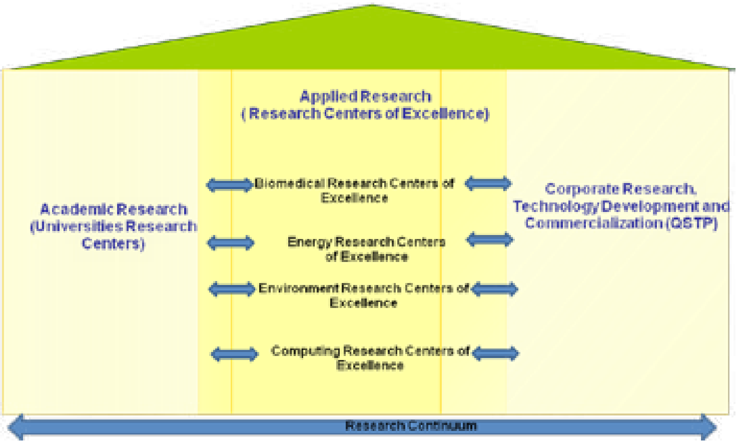

Figure 2. Qatar Research Institutes with focus on Applied Research

- Fundamental research is conducted by the branch campus universities at EC, under budgets provided by Qatar Foundation or through project grants from the Qatar National Research Fund
- Applied research will be mainly led by the three Qatar Research Institutes being established by Qatar Foundation and Sidra Medical and Research Center will principally undertake applied research
- Technology development and commercialization is conducted by companies at Qatar Science & Technology Park and centers established by the park.

Partnership and Integration

Qatar has the twin aims of rapidly launching major research activities and developing its own indigenous scientific institutes – all of the highest international standard.

To achieve this Qatar Foundation has adopted the strategy of partnering with renowned overseas institutes to establish research and training programs at Education City, while simultaneously building its own research institutes and training local citizens to take on leadership positions.

It also works with relevant external organizations in Qatar such as Hamad Medical Corporation and Qatar University, to achieve alignment and integration between the country's research efforts.

The Research Division promotes science at Education City in two main ways: by "sponsoring" the research programs of its member organizations including the seven branch campus universities, and by "establishing" its own Qatar Research Institutes.

In sponsored research, the member organization formulates the scientific plan, manages the program and employs the personnel. Qatar Foundation funds the program and retains an oversight role. In its Qatar Research Institutes, Qatar Foundation itself employs the staff and manages the operations.

As an example the Qatar Biomedical Research Institute will focus on stem cell research. In this regards, QF formed an agreement with the James A. Baker III Institute for Public Policy to develop the policy for stem cell research. Partners for specific research programs are also under discussion. Meanwhile the division has organized internships for several Qatari scientists at stem cell labs in Qatar and abroad, as part of their career development to eventually become leaders at the Qatar Biomedical Research Institute.

In this way Qatar will be able to rapidly engage in stem cell research of an international standard, while gradually building the capacity of its own scientists and institutes.

A Culture of Critical Thinking

That is not all. Qatar National Research Fund—another strategic component of the Foundation's R&D pillar—supports research around the world. The Fund makes grants to local and international researchers under the condition that the topic fits Qatar's national research strategy and research priorities and involves a research partner based in Qatar.

Qatar Research Institutes that will conduct applied research in a multidisciplinary and collaborative approach on some of the most pressing challenges facing Qatar and the world such as cancer diabetes, clean energy environmental protection and seizing the opportunity of the digital age.

Sidra Medical and Research Center, a unique academic medical center with a $7.9 billion endowment set to open in 2012 to undertake medical education, biomedical research and clinical care with special emphasis on women and children.

Qatar Science and Technology Park to provide support that will enable research and business ventures to materialize in the marketplace. Its programs and services encourage entrepreneurship, advance start up companies, and foster collaboration between its tenants and academic institutions, in Qatar and overseas.

Human Capacity Building

Qatar's leaders know that the country's hydrocarbon wealth, while abundant today, will eventually be exhausted. 'That's why the government is investing so much in high-quality human capital development,' explains Dr. Fathy Saoud, president of Qatar Foundation. 'Human and intellectual capital is a sustainable way to generate wealth, and this is what we are developing at Qatar Foundation.'

The primary mission of QF is to foster the individuals that will form an innovative and knowledge-based society in Qatar.

Placing this mission at the heart of its strategy, QF to develop a sizeable base of local scientists that have the knowledge, skill and opportunity to pursue world-class research.

The two main training programs are the Qatar Science Leadership Program, which accelerates the career development of Qatari scientists recently graduated from university, and the Scientific Research Exchanges Program, which provides opportunities for professional researchers to gain experience in the laboratories at of leading institutes overseas.

Interacting With the Public

Transforming Qatar into a knowledge-based society means not only performing research, but also fostering a community of scientists and a broad culture of curiosity and scientific literacy.

To raise science awareness and engagement, Qatar Foundation's Research Division has established initiatives that promote Qatar's research activities domestically and overseas, engage the local community in the nation's research agenda through conferences and lectures, and communicate that agenda to stakeholders and the public.

- The Distinguished Lecture Series is a program that brings renowned scientists to Qatar to share their experiences and allow local scientists to develop research collaborations with them. Lectures typically consist of a Nobel Laureate describing his or her research, followed by discussion and a networking forum. Since 2008, six lectures have been held.
- International conferences are an important means for scientists to remain abreast of developments in their field, share their findings, and identify opportunities for collaboration—and differentiation—in their work. For the host country, conferences also help to build recognition and credibility of its science programs.

Conclusion

With such a campus, an innovative business model, a growing team of expert researchers and a holistic approach to knowledge development, Qatar Foundation is breaking new ground as it builds a knowledge economy that will unlock the potential of Qatar today and in the future, as well as the wider region and world at large.

It is early days, but Qatar is rising to the challenge of building an advanced economy with a well-thought out plan and strategic funding from its oil and gas reserves. Time is on its side as it quietly leverages this investment into a bright new future. In the meantime, it wants the world to know that Qatar is open for business and that it is rapidly and firmly becoming the regional hub for education and research, thus a typical knowledge based economy.

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LAST WORDS

Invitation to BioVision 2011

Christian Grenier

Discover, Debate, Network

BioVision is the forum for questioning the call of science to serve society. It is an international summit where present and future scientific challenges are debated.

During the last 10 years BioVision has brought together scientists, industry, policymakers and NGO leaders from all over the world in an endeavour to improve the harmonious integration of progress in life sciences and biotechnology into contemporary society. Fostering reflection, debate and consultation, BioVision is an important player of the Science and Society dialogue.

It is an ambitious yet humble step towards sharing the knowledge and findings of world experts with those who can then ensure such knowledge is passed on and used in the broadest sense possible.

BioVision 2011 in Lyons, France, will be divided into three tracks.

In the Scientific Advances track, scientists at the forefront of their discipline will present their latest advances and a round table will include representatives from civil society, industry and policy makers to debate their impact on Society. Among the themes selected by BioVision Scientific Committee are: How to deal with emerging and re-emerging infectious diseases; Future therapies and human enhancement; can we cure aging; The bio-based industry and Nutritherapy.

The Decision makers' perspective track will bring key leaders from industry, governments, international organizations, civil society to share their insights on major future challenges in health, nutrition and the environment during several plenary sessions. Debates will focus on Creating artificial living; Drugs and developing countries; How we will be fed in 2020; Health: a right for human beings, at any price?

A new track: Business in Science aims at exploring links between scientific research and life sciences industries. The focus will include: The end of the traditional life science industry model: What's next? Worldwide business and economic experts will debate open innovation, digital health, meeting the medical needs of emerging countries.

A new networking tool will be available to participants in order to facilitate contacts and meetings. Thanks to our growing network of international partners, several parallel events will be held during the forum.

By bringing together ideas and fostering discussion among participants, BioVision is a showcase of the contribution of life sciences to major development issues. We will therefore ensure that the content of the debates to reach as wide an audience as possible, in particular through our website.

The BioVision Forum also continues to open its doors to younger generations, with the sixth edition of BioVision.Nxt: a hundred promising researchers mainly from the academic world, but also from innovative businesses, are invited to Lyon to participate in the forum. These young people come from all over the world, and are selected for the outstanding results they have achieved in their work. They will meet during the forum, participate actively in the sessions, and compare their thoughts and findings with others in the forum.

We have been working closely with BioVision.Alexandria to prepare this 7th edition, particularly concerning the speakers and BioVision.Nxt.

We will be honoured to welcome you at BioVision 2011. More information on the programme and the speakers will be available from September on our website http://www.biovision.org.

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