Ethics of science and technology

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Explorations of the frontiers of science and ethics

UNESCO

United Nations
Educational,
Scientific and
Cultural Organization

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Henk ten Have

UNESCO and Ethics of Science and Technology

Introduction

When the United Nations Educational, Scientific and Cultural Organization (UNESCO) was established 60 years ago, its Constitution declared that peace must be founded upon the intellectual and moral solidarity of mankind. Julian Huxley, the first Director-General, pointed out that in order to make science contribute to peace, security and human welfare, it would be necessary to relate the applications of science to a general scale of values. Guiding the development of science for the benefit of humanity will therefore imply 'the quest for a restatement of morality ... in harmony with modern knowledge' (Huxley, 1946). Since its foundation, UNESCO has been concerned with moral issues in relation to science. From the 1970s onwards, the emergence of the life sciences in particular has led to international examination of bioethical questions. This global focus on bioethics was institutionalized in 1993 with the establishment of the International Bioethics Committee (IBC) and a work programme and budget for international

activities. The programme was expanded in 1998 with the foundation of the World Commission on the Ethics of Scientific Knowledge and Technology (COMEST), which addresses other areas of applied ethics such as environmental ethics, science ethics and technology ethics. Since 2002, UNESCO has also been coordinating the activities of international bodies in the area of bioethics through the Inter-Agency Committee on Bioethics. In the same year, UNESCO's 191 Member States decided that ethics should be one of the priorities of the Organization.

The current revolution in science and technology has led to the concern that unbridled scientific progress is not always ethically acceptable. The need to establish common values and benchmarks, as well as to promote ethical principles and standards to guide scientific progress and technological development, is becoming increasingly acute, especially in developing countries that do not equally enjoy the benefits of scientific and technological advances. UNESCO's work in ethics of science and technology reflects these global concerns. It examines such progress in light of ethical considerations rooted in the cultural, legal, philosophical and religious heritage of the various human communities.

UNESCO's activities in ethics of science and technology take many forms and cover much ground. They include, for example, drawing up recommendations for decision-makers and developing ethical guidelines, standards and legal instruments, such as the Universal Declaration on the Human Genome and Human Rights (1997) and the International Declaration on Human Genetic Data (2003). UNESCO also helps to develop regional networks, builds capacity, promotes ethics in science education and provides educational materials. Furthermore, it performs an essential 'ethical watch' function and plays an important role as a catalyst and think tank, informing public opinion on the human rights implications of scientific and technological progress.

Linking science and policy: COMEST

In 1998, UNESCO established the World Commission on the Ethics of Scientific Knowledge and Technology (COMEST) to advise the Organization on issues concerning ethics of scientific knowledge and technology. This 18-member body is composed of prominent and independent scientists from various disciplines and other experts from different regions of the world. They are appointed by the Director-General of UNESCO for a four-year term. The COMEST Secretariat is located within the Division of Ethics of Science and Technology.

COMEST is specifically mandated to be an international advisory body and an intellectual forum for exchanging ideas and experience; encouraging the scientific community to examine fundamental ethical questions and to detect the early signs of risk situations. It formulates ethical principles that can shed light on the various choices and impacts brought about by new discoveries. It advises decision-makers on policy issues and promotes dialogue between the international scientific community, government and the public at large concerning sensitive areas such as sustainable development; freshwater use and management; energy production, distribution and use; outer space exploration and technology; as well as issues of rights, regulations and equity related to the rapid growth of the information society.

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The Commission executes its mandate by bringing together experts to study specific problems and disseminates the results of their analysis through publications. Areas such as ethics and space technology, ethics and energy, and ethical issues in relation to water use have been examined in the past, and have led to widely disseminated publications (Audouze, 1997; Kimmins, 2001; Pompidou, 2000; Selborne, 2000). The most recent publication concerns the Precautionary Principle; because this principle is controversial from an international perspective, a group of experts was formed to analyze the concept and its applications in diverse settings in order to clarify possible

misunderstandings (COMEST, 2005b). COMEST also organizes a public session every two years, bringing together scientists, ethicists, lawyers and policy-makers to discuss salient ethical questions in science and technology. Such well-attended conferences are organized in different regions of the world, not only to provide a platform for global concerns but also to stimulate the ethical debate and the creation of networks of experts in these regions. Recent conferences have taken place in Rio de Janeiro (2003) and Bangkok (2005) (COMEST, 2005a). The forthcoming meeting will be in Africa in 2007.

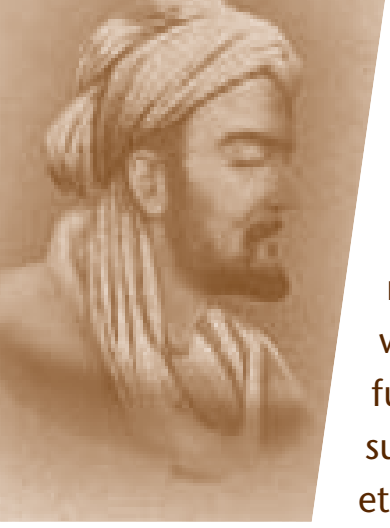
Ethics education

The Framework for Action of the World Conference on Science (Budapest, 1999) states that ethics and the responsibility of science should be an integral part of the education and training of all scientists and that they should be encouraged to respect and adhere to basic ethical principles and responsibilities of science. In 2002, the Division of Ethics of Science and Technology and COMEST organized a Working Group on the Teaching of Ethics that has provided advice on how to integrate ethics and responsibility in scientific training. This Working Group has produced a report on the teaching of ethics, which includes a survey of existing programs, an analysis of their structure and contents, and detailed curriculum advice on how to integrate ethics, history, philosophy and the cultural impact of science into scientific education (COMEST, 2003). This report has been the basis for the Ethics Education Programme launched in 2004.

During the 32nd UNESCO General Conference (2003), many Member States expressed the need to initiate and support teaching programmes in ethics, not only in bioethics but in all scientific and professional education. Teaching in this area varies greatly between regions and countries, and requires that attention be given to moral issues that are relevant to specific regions. As a first step, it is important to collect data on ethics teaching. In

order to establish a database of ethics teaching programmes, standardized forms have been developed to describe teaching programmes so that the substance of each programme can be examined and various programmes analyzed and compared. Within a group of countries, experts are identified who are actually teaching within a university setting. The experts are invited to take part in a regional meeting; in advance, they are invited to provide data on their programmes and to return the forms so that these can be discussed during the meeting. Often, it is the first time that experts have insight into the programmes taught by their colleagues. The meeting provides an opportunity for data to be clarified and discussed, difficulties identified and problems discussed with colleagues. With the empirical data obtained and clarified, the next step is taken: exploring future needs and how UNESCO can help to promote ethics teaching. To date, expert meetings have been organized in Budapest (October 2004), Moscow (January 2005) and Split (November 2005). Approximately 100 teaching programmes have been approved and will be entered into the Global Ethics Observatory (GEO) database. In 2006, further meetings are planned in Asia and the Arab region. One common finding so far is the vulnerability of ethics teaching programmes. Often, the programmes are taught by enthusiastic teachers but lack a firm institutional basis and do not create a future generation of ethics teachers. Another finding is the absence of cooperation between nations. International cooperation between experienced teachers in neighbouring countries could create programmes with more impact and sustainability, but awareness of other programmes and willingness to work together in this area need further stimulation.

Another feature of the Ethics Education Programme is the Advisory Expert Committee on the Teaching of Ethics. This ad hoc Committee, composed of members of IBC and COMEST as well as a representative of the UNESCO Chairs in Bioethics, the Third World Academy of Sciences (TWAS) and the World Medical Association (WMA), will assist UNESCO in the area of ethics teaching. One of its first projects will be the development



of a proposal for a core curriculum in bioethics, on the basis of the recently adopted *Universal Declaration on Bioethics and Human Rights*. As soon as such a proposal has been developed, multimedia resources will be created in order to assist scholars who want to establish teaching programmes in bioethics. In future, similar efforts can be made for other areas of applied ethics, such as environmental ethics and science ethics and engineering ethics (examples of which can be found in the GEO database).

Research

As the leading international agency in ethics in science and technology, UNESCO explores new and emerging issues in this field, such as nanotechnology and, in bioethics, human cloning, stem cell research and pre-implantation diagnosis. Ethical reflection is often criticized for being too late and, therefore, futile. It is important to establish anticipatory mechanisms for identifying and analyzing scientific and technological advances that will give rise to ethical questions in the near future. Sophisticated and innovative technologies are usually developed in a limited number of countries, but the impact and consequences of these technologies are sooner or later felt by all countries. In such cases, it is appropriate that all Member States of UNESCO be made aware at an early stage of the possible ethical issues in regard to new scientific knowledge and technology. A good example is nanotechnology. A group of experts has been brought together by UNESCO to study this issue; they are researching the state-of-the-art in science and ethics. The experts' papers will be published in a book aimed at making policy-makers aware of the ethical implications. They will also assist the Secretariat to draw up a policy paper with suggestions for possible actions by UNESCO. This policy paper will then be submitted to COMEST for advice and analysis. Another example is ethics in relation to space technologies. UNESCO, together with the European Space Agency (ESA), is organizing public conferences focused on ethical issues of space sojourns (October 2005) and space exploration (October 2006) (UNESCO, 2005a).

Raising awareness

UNESCO strives to create a better understanding of the major ethical issues raised by science and technology and supports analysis and discussion of those issues internationally, regionally and nationally. An essential part of this work is raising public awareness and stimulating public debate. This is important for two reasons. First, ethics is of interest to policy-makers because of public concern. Because there is public concern and debate on issues such as cloning, research involving human beings, transplantation, nuclear energy, environmental pollution and global warming, ethics has been placed on the national and international agendas. Ethics is no longer solely the concern of scientists, engineers or health care professionals. It has therefore transcended the exclusive domain of experts, showing that science is first of all a public enterprise, a social activity and a cultural good. Second, scientific developments often affect all people. This is clear in medical research, which is increasingly dependent on the cooperation of large numbers of patients and healthy volunteers, often in international trials. This implies that the interests of science and research should be balanced with the interests of participating people, precisely because human rights and freedoms can be at stake. Public debate and awareness raising are therefore important to make it clear that science and technology are advancing within an ethical framework of respect for human dignity and human rights. They also show that scientists have responsibilities towards society and do take into account the possible effects of their work on society, for example as regards protection of the environment, promotion of justice, and prevention of biohazards and bio-events.

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That is why the Division of Ethics of Science and Technology organizes 'Ethics around the World', a series of thematic rotating conferences to disseminate information and promote interaction and networking among national and international experts. The objective is to stimulate debate at national and regional levels to build up the participation of civil society in the debate.

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These conferences, which are organized jointly with national commissions for UNESCO, UNESCO field offices, and academic or research centres, usually feature one or two keynote speakers (often members of IBC or COMEST), followed by open debate. Over the last two years, 'Ethics around the World' conferences have been held in the Netherlands, the Islamic Republic of Iran, Lithuania, Mexico, Argentina, the Russian Federation, Portugal, Turkey, the Republic of Korea, Indonesia, China, Estonia and the Philippines. During 2006, 'Ethics around the World' conferences will take place in New Zealand, the Democratic Republic of Congo and the Dominican Republic.

Awareness raising will also be carried out by producing and disseminating publications. An explanatory brochure has been made on ethics and human cloning; this publication has been produced in the six official languages of UNESCO (English, French, Spanish, Arabic, Russian and Chinese) (UNESCO, 2005d). A similar brochure focusing on ethics and nanotechnology is in production.

Global Ethics Observatory

In order to provide Member States with proper tools for reflection and appropriate means for coping with emerging ethical challenges in science and technology, UNESCO is becoming more involved at national and regional levels. The establishment of a Global Ethics Observatory (GEO) will be such a tool. GEO is constituted by at least four databases. The first database ('Who's who in ethics?') will present data on experts in various areas of ethics. A questionnaire has been developed and mailed to experts in all regions of the world. The database will allow searches for different types of experts according to country, area of expertise, experience and keywords. The second database will include data of institutions such as ethics committees (at different levels: local, national, regional, international), departments and centres in the area of ethics, and associations and societies in ethics. This database, like the

others, will cover all areas of applied ethics: bioethics, nursing ethics, law and ethics, social sciences and ethics, science ethics, environmental ethics, engineering ethics, etc. In due course it will also present all data in the six official languages of the Organization. The third database will present the descriptions of ethics teaching programmes developed through the Ethics Education Programme, described above.

Efforts are now focused on constructing the layout of the fourth database. This database aims at providing information about legislation, guidelines and policies developed in Member States in relation to the ethics of science and technology. It will not merely provide the texts of such legal regulations, but, more importantly, will identify the structure, set-up and contents, which will be instructive for other countries that are contemplating drafting legislation in the domain of ethics, for example in connection with research involving human beings or with ethical principles in science in general. In order to provide useful information that can guide the drafting of legislation, the database will provide examples; it will therefore be necessary to abstract or excerpt the main characteristics of existing legislation. A team of legal experts will examine the question of how international legislation can be made comparable and will develop a methodology for the construction of this database. Additional databases may be included in GEO in the near future, for example a database with existing codes of conduct for scientists.

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Building national capacity and international cooperation

The objective of the UNESCO programme is to identify ethical issues that are relevant to the various regions of the world in an effort to determine and implement appropriate strategies for encouraging ethical reflection at regional and sub-regional levels, and for strengthening national capacities and

international cooperation in bioethics. For these efforts to be successful, it is essential to take into account the legal, cultural and religious traditions in the Member States.

This is why the *Universal Declaration on Bioethics and Human Rights* advocates the establishment of independent, multidisciplinary and pluralist ethics committees at national, regional, local or institutional levels. The purpose of these committees is to foster the exchange of ideas and information, support decision-making, develop tools for standard setting, and strengthen coordination and contacts among experts and institutions (e.g. through databases). They also reinforce the role of UNESCO as an international clearing house for ethical issues. Ethics committees will also be among the most important intermediary bodies for the implementation of the normative instruments adopted by the Member States. In many countries, there are bioethics committees at various levels of government. However, in the majority of Member States, such committees do not exist at the moment. UNESCO has a programme to support the establishment and operations of bioethics committees – the ABC (Assisting Bioethics Committees) programme. Through a series of practical guidebooks, information is provided about how to establish such committees, and how to function when a committee has been established (UNESCO, 2005b, 2005c). New guidebooks will address the topics of educating committee members and public outreach of committees. Task forces of experienced committee members in Member States with operational committees will assist those countries that are in the process of establishing committees. In future, similar efforts will be focused on national committees with a mandate comparable to COMEST, covering areas of ethics of science and technology beyond bioethics. In some countries, for instance Hungary, such national 'COMEST-type' committees have been established, and their experiences can be useful for other Member States.

The Avicenna Prize for Ethics in Science

Created in 2002 by UNESCO on the initiative of the Islamic Republic of Iran, this biennial prize rewards individuals and groups who have contributed to high-quality research in the field of ethics in science and technology. It is named after Abu Ali al-Husain ibn Abdallah ibn Sina – also known by his Latin name Avicenna – one of the greatest scientists, philosophers and doctors of the 10th and 11th centuries (UNESCO, 2004). The Prize consists of a gold medal of Avicenna, a sum of US$10,000, and a one-week visit to Iran, during which the prizewinner will deliver speeches at academic gatherings. Candidates are nominated by UNESCO Member States and international NGOs officially linked to the Organization, and the Director-General designates the winner on the recommendation of an international jury. The first Avicenna Prize was awarded in April 2004 to Margaret A. Somerville, an Australian-Canadian Professor of Law and Medicine at McGill University in Montreal. She is also the founding Director of the McGill Centre for Medicine, Ethics and Law, and the founding chairperson of the National Research Council for the Canada Ethics Committee. The second Avicenna Prize laureate (2005) is Abdallah S. Daar. Previously Professor of Surgery at Sultan Qaboos University in the Sultanate of Oman, he is currently Professor of Public Health Sciences and of Surgery at the University of Toronto, Canada, where he is also Director of the Programme in Applied Ethics and Biotechnology and Co-Director of the Canadian Program on Genomics and Global Health at the University of Toronto Joint Centre for Bioethics, and Director of Ethics and Policy at the McLaughlin Centre for Molecular Medicine.

This collection

In this publication we have brought together a selection of writings by the two Avicenna Prize laureates. The following chapters not only give an impression of the breadth of their scholarship but they also provide excellent examples of

the type of research that the Prize intends to promote and disseminate. Professor Somerville analyzes the fundamental problems of contemporary ethics in present-day societies as well as the philosophical questions raised by the modern life sciences. Professor Daar focuses on illuminating specific topics of modern science and technology such as pharmacogenetics, xenotransplantation and regenerative medicine, with special attention to their global impact and implications. We hope that publishing their work in this book will promote ethical reflection in the Member States of UNESCO and will give further impetus to ethics of science and technology around the world.

References

Audouze, J. 1997. *The Ethics of Energy*. Paris, UNESCO.

COMEST. 2003. *The Teaching of Ethics*. Paris, UNESCO.

_____.2005a. *Fourth Session, 23-25 March 2005, Bangkok, Thailand: Proceedings*. Paris, UNESCO.

_____.2005b. *The Precautionary Principle*. Paris, UNESCO.

Huxley, J. 1946. UNESCO: *Its purpose and its philosophy*. Paris, Preparatory Commission of the United Nations Educational, Scientific and Cultural Organization, p. 41.

Kimmins, J. P. 2001. *The Ethics of Energy: A framework for action*. Paris, UNESCO.

Pompidou, A. 2000. *The Ethics of Space Policy*. Paris, UNESCO.

Selborne, J. 2000. *The Ethics of Freshwater Use: A survey*. Paris, UNESCO.

UNESCO. 2004. *Avicenna and the Ethics of Science and Technology Today*. Paris, UNESCO.

_____.2005a. *ECSL/UNESCO/IDEST Symposium on a 'Legal and Ethical Framework for Astronauts in Space Sojourns': Proceedings*. Paris, UNESCO.

_____.2005b. *Guide 1: Establishing Bioethics Committees*. Paris, UNESCO.

_____.2005c. *Guide 2: Bioethics Committees at Work: Procedures and policies*. Paris, UNESCO.

_____.2005d. *Human Cloning. Ethical issues*. Paris, UNESCO.

Chapter 2

Margaret A. Somerville

Searching for Ethics in a Secular Society

Recently, the search for ethics seems to have been everywhere. One has only to pick up the daily newspapers to see the perceived relevance of 'ethics talk' to much of what goes on in our lives as individuals and communities. We are now exploring the ethics of politics and politicians; the ethics of public policy, governmental bureaucracy and public accountability; ethics in academia, business, industry and health care; the ethics of our treatment of animals; environmental ethics; ethics in the media; ethics in sport; the ethics of armed conflict; and the ethics of scientific and medical research and the new technologies resulting from it. This widespread search for ethics can be seen as an early twenty-first century revolution in conscience and consciousness, in the sense of awareness of the need to ask the question 'Is it right?' in a wide variety of contexts. Science and technology is only one of these contexts, but, as many of us have come to realize, it is an especially important one.

* Adapted from Chapter 1 of T*he Ethical Canary: Science, society and the human spirit*. Somerville, M. A. 2000. Toronto, Canada, Viking.

Why has this search for ethics emerged now? In our postmodern, industrialized Western democracies? They are societies characterized by being pluralistic, secular in the public square and politically, and multicultural. These same features also mean that these societies lack a 'shared story' – the collection of fundamental values, principles, attitudes, beliefs, myths and commitments that we need to buy into in order to function as a society, and that we use to give meaning to our communal and individual lives. This story, or societal-cultural paradigm, is the glue that holds us together.

However, at present, in secular societies we are in search of a new story. Some of the factors that have caused the collapse of our old story result from the extraordinary advances in science and technology, whether information technology, the neurosciences, nanotechnology, artificial intelligence or molecular biology and genetics. The possibilities these advances open up are mind-altering, society-altering and world-altering and, depending on how we use them, could radically alter our human nature or even annihilate us. We have become very sensitive to the threats that these new technologies present to our physical existence and our planet. Our contemporary search for ethics shows, I believe, that we are becoming much more sensitive than we have been to their threats to our human spirit – the deeply intuitive sense of relatedness or connectedness to all life, especially other people, to the world, the universe and the cosmos in which we live; the intangible, invisible, immeasurable reality that we need to find meaning in life and make life worth living. In short, the human spirit is the metaphysical reality (that which is beyond the physical) that we need to fully live fully human lives.

Our shared story has always focused on the two major life events of each human life, birth and death. Indeed, the general level of respect for human life that permeates a given society is largely determined in these contexts. We also structure both our rational and non-rational knowing in a coherent framework through focusing on human beginnings and endings. Many

rituals of celebration and mourning have human beginnings and endings as pivotal motifs. We use these rituals to create the sense of community that we need to enrich our experience or to sustain us, both at the time of these events and more generally.

Contemporary ethics talk often focuses on the possibilities that new scientific developments have opened up in relation to birth and death. At one end of the life span, we are faced with a stunning power that no humans in previous ages ever possessed: the potential to alter, through the use of a combination of genetic and new reproductive technologies, the very basis of human life and its mode of transmission. As discussed in greater detail in the next chapter, the possibilities presented by these technologies include *in vitro* fertilization; cloning human embryos; cloning our adult selves; using ova from aborted fetuses to produce children whose 'mother' was never born; and designing our progeny through genetic manipulation in ways that range from choosing certain physical characteristics – such as height or eye or hair colour – to dramatically augmenting their intelligence through a so-called smart gene and even creating disease-proofed children. At the other end of the life span, we face issues of the allocation of very expensive life-prolonging treatments; xenotransplantation; withdrawal of life-support treatments from terminally ill people; and euthanasia.

In the past, we wove the metaphysical fabric in which we wrapped the events of birth and death mainly using the resources that we found in religion. And we bonded together through a shared religion – both in the present and with past and future generations. After all, the word *religion* comes from *re-ligare* – to bind together. The great religions have traditionally given us a compelling shared story, allowed us to pass on our most important values to future generations, enabled us to form and live in families and communities, and stimulated and extended our human imagination. But in the mid-1970s we began to transfer our 'collective faith' from religion to the extraordinary new science that was emerging. In particular, modern

medical 'miracles' held out hope, if not of immortality as most religions do, at least of delayed mortality. This new science radically altered our perceptions of the nature of human life, its transmission and its passing. Consequently it forced us to re-evaluate the meaning we give to the major life events of birth and death, and, therefore, the nature of the society we will create. Moreover, in postmodern, secular, pluralist societies such as Canada, by definition, religion – or at least traditional, institutional religion – can no longer be used to create our shared story, at least not as a sole mechanism. Quite apart from the fact that today many people do not adhere to an institutionalized religion, even those who do are likely to practise one that is different from that of their neighbours. And yet for many people, religion remains an important lens through which to see life and the values and meaning that we attribute to and find in it. The secular-societal paradigm we create must, therefore, as we see articulated in all declarations of fundamental human rights, accommodate and respect people's freedom of conscience and religion.

One of the substitute forums for religion that has emerged in secular societies in the last fifty years is medicine and health care. Because we all personally relate to and identify with health care, it is a very important forum for creating values, implementing those values and carrying them forward. Health care is also the forum in which new scientific developments and the ethical issues they raise are encountered by people most directly and personally – and often most dramatically. Within this primary forum of health care, we will work out the ethics that should govern these new technologies and decide what we may, must and must not do with them. Thus health care is an ethics laboratory for societies like Canada. Our decisions about health care, especially when those decisions concern new scientific and technological developments, are never just about health care. They have a much wider impact on society as a whole.

For example, extraordinary new advances in medical science have shocked us into recognizing that we do not have consensus about the values that we

need in order to address the immense ethical issues these new technologies raise. We have also recognized that these issues must be accommodated within our general societal paradigm; we would deal with them in isolation at our peril. The search for ethics is part of this accommodation process.

Our search for ethics is also related to a change in the basis of trust in our societies. Jay Katz, a psychiatrist and law professor at Yale University, has described this as a shift from 'blind trust' ('Trust me, because I know what is best for you') to 'earned trust' ('Trust me because I will show that I can be trusted'). Just as we can no longer assume that there is consensus on the values we will uphold, likewise, we can no longer assume the presence of trust in our society and its institutions. Rather we must take steps to ensure that it is present.

One way to view the search for ethics, then, is as the search for societal values in a secular democracy. In this type of society, we no longer automatically have access to a received set of values through a shared religion, and we can no longer impose values or assume there is consensus on them. We must, rather, find and agree on these values and a very important context in which we are seeking to do this is in relation to how we should and should not use the new science.

I want to identify some particular changes that have resulted from the overall shift in the general societal context I have just described, changes that are powerful forces in precipitating the search for ethics. These include a move to intense individualism; the adoption of a situational ethics approach in searching for shared values; the impact of the media; the increased use of law in resolving disputes about values; the effects of the unprecedented powers provided by new science and technology; the emergence of new fears; the impact of a 'gene machine' mind-set on our societal-cultural paradigm; an intolerance of mystery; a loss of our sense of the sacred, and of wonder, awe, play and humour; the emergence of a market-place approach to values and, subsequently, post-materialism. Let us examine some of these in more detail.

Secular Western societies are based on *intense individualism* – possibly individualism to the exclusion of any real sense of community. In fact, one way to view intense individualism is as the institutionalization of a sense of disconnection from each other. And yet we humans cannot live fully human lives without having a sense of belonging to a community – whether the smallest community of family, the larger one of our immediate friends, peers, neighbours, village or city, or the even larger one of society, as a whole. Many of us have difficulty eliciting this sense that we are part of something larger than ourselves. Indeed, Daniel Yankelovich, a leading survey researcher in the United States whose work focuses on changes in the values of the American population, found that the fastest growing trend was people's longing to belong to something larger than themselves, a yearning for some form of transcendence.

Did the adoption of intense individualism mean that we lost a sense of community or did we reject a sense of community and adopt intense individualism to fill the void? If the latter is correct, why would we reject community? Might we have confused community with 'the system' that we use to run our society – especially the bureaucracy that makes up this system – and rightly rejected the notion that a system would ever be considered more important than individuals or take priority over them? But there is a difference between a system that runs a community – including when that community is a society – and a community, itself. The latter is a living entity; it has, for want of a better word, a soul. The former does not. Sometimes a community might take precedence over individuals; a system should not.

John Ralston Saul in his book *The Unconscious Civilization* describes a phenomenon he calls 'corporatism'. He points out that although the foundation of democracy is that each person's voice should be heard and each person's vote should count, modern democracy functions in response to interest groups – corporate entities ranging from grassroots groups to transnational industries – who advocate approaches that favour them but

not necessarily the society as a whole or the common good. The individual is powerless – his or her voice is not heard and a vote does not count. Is there a relationship between this development and intense individualism? Could intense individualism have given rise to corporatism – individuals coalesce as individuals in order to exercise power to their own advantage? Is corporatism an example of collective intense individualism?

We can see the impact of intense individualism in relation to science and medicine in some of the approaches taken, for example, to the new reproductive technologies and euthanasia. If we give pre-eminence to the values of personal autonomy and self-determination, and competent adults' rights to decide for themselves, the result is highly likely to be a judgement that most applications of reproductive technology and euthanasia are acceptable. But respecting the rights of the individuals who make up a society, important as this is, is not always sufficient to protect the society itself. Sometimes, in carefully justified instances, to do so we must give priority to the needs of the community over the claims of individuals.

Intense individualism can also be connected with a loss of respect for ourselves, others and our environment. *Re-spect* comes from the Latin word meaning to look back on. If we cannot see ourselves in context, if we lose our ties with the past – if we fail to look back – progress becomes synonymous with amnesia. The philosopher Mark Kingwell calls this the great fiction of the 'eternal now'. We fail to remember at our ethical peril. Respect is the mechanism through which we remember, and it requires us to see ourselves in a larger context than just ourselves. Intense individualism functions from the opposite basis and is, therefore, incompatible with this type of respect. (One area where exploration of the conflict between respect and intense individualism could provide insights is that of the allocation of and access to health-care resources.)

Intense individualism is probably, in part, a response to globalization. Because the vastness of the connection that

globalization represents can make us feel so small, insignificant and anonymous, we seek refuge for our ego – reassurance that we exist and, perhaps, matter – in intense individualism, tribalism or both. The danger of tribalism, which in some ways is also a collective form of intense individualism, can be seen in many of the horrific armed conflicts and massacres in various parts of the world in the last decade. Such examples make us realize that intense individualism can be an attempt to fulfil a need to take control in a situation in which we feel abandoned and afraid because we have an overwhelming sense that indeed we are only an individual – we are alone.

There is, however, a paradoxical side to intense individualism. People who espouse it (strong civil libertarians, for instance) can bond through their belief – it can function as an ideology binding them together, as a substitute for the bonding that religion used to provide. Moreover, the experience of going through a stage of intense individualism might be the template for a new – or a return to a very old – form of community. This change would occur if we moved beyond the focus of intense individualism just on individual rights to an equal and balancing focus on individual responsibilities, especially for those people who are vulnerable, for community and for the common good. A concern raised by the predominance of intense individualism is that it has caused us to lose a sense of the common good and of what is required of us if we are to protect and promote the common good. The current search for ethics could indicate the emergence of a focus on individual responsibilities as well as rights and a renewed willingness to act in the interests of furthering the common good.

In contrast, if we apply intense individualism to our search for values, they can be reduced to simply what I as an individual prefer, which means that it is very difficult to find consensus and, as a result, to form community and protect the common good. The political scientist Francis Fukuyama, in his controversial book *The Great Disruption: Human Nature and the Reconstitution*

of Social Order (with at least some of whose arguments and beliefs we might take issue), sums up this phenomenon as 'moral individualism' resulting in 'miniaturization of the community'. But for the purposes of the line of argument I want to develop, the most important effect of the loss of consensus on values is the adoption of a situational ethics approach. In taking a situational ethics approach to the formation of values – adopting moral relativism – so that we can keep all our values' options open, we seem to have lost the ability to agree that anything is *inherently wrong* – that is, wrong no matter how much good could come from doing it.

But can we in practice implement a view that something – for instance, human cloning – is inherently wrong in a society that has no absolute moral rules or no external source of authority for those moral rules that it does have? Can we believe in a moral absolute, even if we are not religious and even if we do not believe in a supernatural being as the ultimate authority? I propose we can do this by accepting two values, which are probably two sides of the same coin, as absolutes. First, we must always act to ensure profound respect for all life, in particular, human life; second, we must protect and promote the human spirit, which I defined earlier in this chapter. If our development or use of any given scientific technology, for example, would seriously harm the fulfilment of either of these two values, it is inherently wrong. I return to this theme in the following chapter.

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Another change from the past is that we are *media societies*. This, in turn, has changed the nature of the public discourse through which we create the shared concepts, ranging from values to laws, that govern our collective life. We are the first age in which our collective storytelling takes place through television – and now, increasingly, the Internet – and, consequently, at a physical distance from each other. We do not know how, in the long run, this change will affect the stories we tell each other in order to create our societal-cultural paradigm. Creating our 'shared story' through the media may, moreover, alter the balance between the various components that go to make it up. For

example, with our current fear-attraction-obsession reaction to death, we may engage in too much 'death talk' and too little 'life talk', or too much despair and horror and too little hope and joy. Moreover, the unprecedented, almost daily exposure of virtually everyone in the society to violence, cruelty and death – seeing the horrors of war, for example, each night in our living rooms – may overwhelm and dull our sensitivity to these atrocities and to the awesomeness of death and, similarly, of inflicting death, whether in war or by euthanasia. The adverse effects of this phenomenon are often discussed, but we need to be especially aware of its impact in the context of doing ethics.

Our frequent failure to take into account social issues in doing ethics is also connected with the increasing use of the media as the means through which we engage in our societal dialogues. The media encourage us to focus on the individuals whom we can see and listen to. For instance, it is difficult to present the argument on television that in governing the new reproductive technologies we must put future children at the centre of the infertility business and consider what is best for them, rather than simply what the person seeking to use this technology wants, or what investors in fertility clinics promote as 'good for business'. It is much easier to show a happy mother and a beautiful child who resulted from using this technology, thus making the case for such use, than to show its risks and harms, especially to important human values such as those governing parent-child relationships.

We face the same dilemma in arguing against euthanasia. It makes dramatic, emotionally gripping television to feature an articulate, courageous, forty-two-year-old divorced woman who is dying of amyotrophic lateral sclerosis, begging to be allowed to have euthanasia made available, and threatening to commit suicide while she is still able if she is refused such access. It is much more difficult to show the harm to important societal values, such as respect for life, and to the institution of medicine, such as loss of trust in doctors, that legalizing euthanasia would cause.

In short, the arguments against reproductive technology or euthanasia that are based on the harm they would do to society are especially difficult to present in the media. They do not make dramatic and compelling television. Visual images are difficult to find; we do not personally identify with either the arguments or the people presenting them in the same way we do with those of happy parents playing with children produced through reproductive technology or dying people who seek euthanasia; and society cannot be interviewed on television and become a familiar, empathy-evoking figure to the viewing public.

In order to identify and articulate the values that we need and can share, we must engage in 'values talk'. Our places of religious worship used to be our main forums for engaging in these discussions. But values talk has been transferred to the media as 'ethics talk'. This ethics talk is frequently interwoven with 'law talk' concerning the same issues.

The role of the legal process (and, probably, of law) in forming our societal values has also changed. Matters such as reproductive rights or rights to refuse medical treatment that would have been largely the subject of moral or religious discourse are now explored in our courts and legislatures, in particular through concepts of individual human rights, civil rights and constitutional rights. When this happens, the cathedrals of a secular society – its highest courts and parliaments – become the forums in which the talk that forms societal values takes place. Consequently, it is not surprising that many of the issues surrounding new scientific developments that evoke widespread public discussion, hope and concern are also, in one form or another, ending up in the courts. For instance, in some countries, people are currently arguing in court about the patenting of human DNA and other life forms, including genetically altered animals; others are seeking injunctions against the release of genetically engineered micro-organisms into the environment; and products-liability law is being used to require the labelling of genetically altered food.

We have become legalistic societies, and this change is connected with a loss of consensus on values, probably intense individualism and the impact of media. Law provides a bottom line, working consensus on values, even if in substance we still disagree. Law is also the most powerful way for individuals to challenge the state and has a very prominent role in establishing the values and symbolism of a secular society. People who are seeking to change these values and symbols use debates such as those on reproductive technologies, abortion and euthanasia as opportunities to further their goals. They do this through taking test cases to the courts and by advocating for changes in legislation. The response of those who oppose these changes can often be to propose harsh measures – for instance, framing them in criminal law – to reject the new values and affirm the old. (For example, legislation specifically criminalizing the transmission of HIV in some American states indicates a backlash by those with conservative values against society's acceptance of homosexuality and tolerance of drug use. But these people might also see enacting such laws as a way to affirm values that are threatened by this acceptance and tolerance.)

It might also be that taking test cases to the courts is some people's way of forming community, somewhat paradoxically, out of intense individualism. Being committed to individual rights – especially those that confront traditional conservative values, such as women's rights to equal pay for work of equal value or the right to marry for same-sex couples – can form the basis for a collective identity, usually one based on "minority status." This identity and the shared values that underlie it can be affirmed through successful litigation. These cases might also be showing a further shift in the locus of our decision-making about societal values. The locus of such decision-making has moved from religion and the clergy to the legislatures and politicians and now to the courts and judges. It is interesting to speculate whether there could be another shift and, if so, where this would be.

Yet another reason why the search for ethics has emerged now is that the new science has moved us *from chance to choice* in many matters – for instance, reproduction. With choice comes the responsibility to use that choice ethically. Doing so requires two kinds of courage: the courage to go forward with the new science and technology when it is morally and ethically acceptable to do so, and the courage to exercise restraint when it is morally and ethically required.

Fear also plays an important and complex role in our responses, both as individuals and as a society, to new scientific developments. Sometimes the fear we experience is unjustified. But sometimes a moral anxiety or an ethical intuition is at the base of our fear and should be heeded. Often we deal with fear by seeking to take control over the situation that elicits it. Consequently, we are likely to adopt new scientific developments that we see as giving us control and to reject those that we see as the source of our fear. We need to carefully research how fear affects our individual and societal psyches and, as a result, our assessment of what is ethical in relation to new scientific developments.

The fact that we are very *intolerant of mystery* can also cause ethical difficulties. Sometimes, we eliminate mysteries by converting them into problems. For example, if we convert the mystery of death into the problem of death and seek a technological answer to that problem, a lethal injection, that is, euthanasia, can be seen as a solution. An inability to live comfortably with uncertainty – which is a variation on discomfort with mystery – can also cause us to adopt simplistic, reductionist approaches to very complex realities. Genetic reductionism – the view that we are nothing more than the expression of our genes – is a good example in this regard. Often these approaches lead us astray ethically.

Similarly, many of us have *lost access to a sense of the sacred*, including the notion that we, as human beings, are sacred in any meaning of this term. There are multiple causes of this loss over the last half-century, including our extraordinary scientific

advances. By a sense of the sacred, I mean the recognition and protection of the human spirit – a sense of what I call the *secular sacred*. This might be more a new label or awareness than a new reality. For instance, we are using this concept often without recognizing that we are doing so to come to a new realization about what is required for respectful human-Earth relationships.

New genetic discoveries and technologies have, along with new reproductive technologies, had a major impact on our sense of the sacred. They can lead us to believe that we understand the origin and nature of human life and that, because we can, we may manipulate – or even 'create' – such life. If we transfer these same sentiments to the other end of life, they would support a view that euthanasia is acceptable, that is, if we can create life we may dispose of it. In other words, we can regard the current movement for the legalization of euthanasia as a correlative development with the new genetics, and its emergence, therefore, as expected. According to this view, it is not an accident that we are currently concerned with both eu-genics ('good' genetics – good at birth) and eu-thanasia ('good' death – or, perhaps, good at death, that is, of no trouble to anyone else). We could even expand this connection between genetics and euthanasia. This expansion could stem from a new perception that we have the ability to ensure our genetic immortality – seeing ourselves as an immortal gene collection – and, as a result, we could reduce somewhat our deep anxiety about the annihilation presented by death. Indeed, a recently emerged group, the transhumanists, whose members include some recognized scientists, believe that eventually the new science will enable us to attain immortality.

Our new genetics has also informed us of the connectedness of all life and of the vast amount of genetic heritage that we share with other animal species. This knowledge has led some to ask why we should regard ourselves as sacred if we do not regard these other species as sacred. In fact, Princeton bioethicist Peter Singer has given a label to the practice of

distinguishing between humans and other animals. He calls it 'speciesism' – a form of wrongful discrimination. Some people, especially those with traditional religious beliefs, are outraged by equating humans with other animals. I suggest that we should see all life as sacred – that is, as requiring profound respect – but human life as demanding a special degree of respect.

The frameworks that we use to structure our knowledge, in general, have always been influenced by scientific advances. For instance, Darwin's theory of evolution and the survival of the fittest has affected fields as diverse as sociology, psychology, political science and economics. Advances in genetics and molecular biology are likewise influencing fields well beyond the borders of the science of genetics. New schools of thought that are influenced by genetics are emerging. These new ideas can challenge our traditional concepts of what it means to be human and what is required to respect human life. For instance, sociobiology asks us to see the characteristics that we have usually identified as the unique markers of being human and as differentiating us from the other animals – namely, our most intimate, humane, altruistic and moral impulses – as also being the products of the evolution of our genes. At a macro-genetic level, deep concern about overpopulation of the Earth, unlike the fears of extinction of the human species through underpopulation in earlier ages, might have thrust us towards losing a sense of sacredness in relation to human life.

The new science can, however, be linked with eliciting a sense of the sacred; it just depends on how we view it. For example, rather than viewing the new genetics as a totally comprehensive explanation of life, we can experience it as deepening our sense of wonder and awe not only at that which we now know, but even more powerfully at that which we now know that we do not know. We can thus see the new genetics and the rest of our science as only one of the lenses through which we are able to search for 'the truth' or, more accurately, 'all truths'. In short, we must place science in a broad human perspective and view

it within this context and not, as we have been doing, place human life in a narrow scientific perspective.

Instead, we should take an approach that is captured in a Japanese saying: As the radius of knowledge increases, the circumference of ignorance expands. The more we know, the more we know the extent of that which we do not know. I often think of new knowledge as a laser beam going out into the dark unknown, opening up a path that we can see and follow but, in doing so, increasing the area of darkness of which we then become aware. Recognition of this darkness, this unknowingness, can connect us with a sense of mystery. Ironically, this means that our scientific discoveries could increase our awareness of mystery, not destroy it. It all depends upon how we view what we learn.

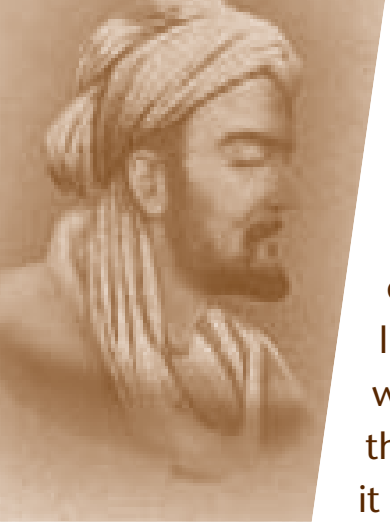
Some people may have a 'So what?' reaction to another change in our societies, yet another group of losses, those of a sense of *wonder* and of *awe*, of *play* and of *humour*. They may even welcome the loss of some of them. But these losses could impoverish our ethical sense. By a sense of play, I mean the childlike, but not childish, feeling that all is right with the world, even though we do not feel we are in control of it. We often make ethical mistakes when we seek certainty – a sense of control – in situations that are necessarily uncertain. Could our intense need for control be connected with a loss of a sense of play? And could this loss result from an undue emphasis on reason to the exclusion of imagination and intuition as ways of knowing? Does this mean that we should be concerned about a loss of the moral imagination and intuition that is essential in doing ethics?

Similarly, should we be concerned about a loss of a sense of humour in its deep meaning of a sense of balance and wise perspective in relation to any particular issue? This sense gives us access to common sense and good judgement, which are crucial faculties in doing ethics, especially in relation to the new science.

We are also highly *materialist, consumeristic societies*, and our search for ethics could help to avert the threats this behaviour presents. Intense materialism creates a danger that people can be equated to products and treated accordingly. For instance, if worn-out people are equated with worn-out products, the people can then be seen simply as a 'disposal' problem. This view would favour euthanasia. Intense materialism would likewise favour the use of human embryos as therapeutic products for the benefit of others. And, if we see our children as products, especially products that reflect on our worth and status – as designer logos are seen to do – we are likely to want to design them to fulfil high standards of physical attractiveness and intelligence through genetic manipulation. This, of course, raises major ethical issues.

Yet another change relevant to the emergence of the search for ethics is the use, in some instances, of capitalism (perhaps as a substitute for religion or even a substitute religion itself, a 'secular religion') in the formation of societal values in secular Western democracies. For instance, some people, including some prominent scientists who do not want to have any explicit ethical restrictions placed on their pursuit of knowledge, argue that the 'morality of the market place' will – and should be allowed to – regulate their science. According to this view, members of the public must be assumed to be moral, and, therefore, it is argued, they will not purchase or use technologies that they consider to be ethically unacceptable. The adherents of this belief propose that the market place can function to ensure ethics: Immoral or unethical uses of new technologies will not be commercially viable. But this approach requires the market to bear a moral weight it is not designed or employed to support. Moreover, even if the market place could act as a moral arbiter, what effect would advertising have on its ability to function in this way?

That said, and without detracting from a belief that market-place morality is an inadequate ethical regulator, the philosophical underpinnings of the market may be changing in a way that



could be ethically relevant. If, as some commentators believe, we are moving from an age of materialism to one of post-materialism with regard to our pre-eminent values, business, especially the scientific-industrial complex, needs a new bottom line, whether we describe this as 'new capitalism', 'the third way', or 'post-capitalism'. This new bottom line will not abandon the component of the old single bottom line, that of profit, but it will integrate it with protection of the environment, concern for maintaining a sense of community and social cohesion, and ethics. The idea that bad ethics is bad business is, it appears, becoming more broadly accepted, not only in theory, but also in practice. It might even be that this fourfold combination will prove to be a 'fourth way', one that takes account of the need to protect and foster the human spirit.

The above discussion leads to an important insight: We are searching for a new world view as a basis for a new societal-cultural paradigm. There are, I propose, three competing possibilities, each of which has a very different relationship to the new science.

The first is the 'pure science' view, which takes a position that science does, or will be able to, explain everything, including those characteristics such as altruism and morality that we regard as distinguishing us from other animals and most clearly identifying us as human. This profoundly biological view of human life is a gene-machine approach. It seeks meaning in human life mainly or only through science and similarly seeks to exercise control through science. Such control can be implemented through the development and use of technologies that scientific discoveries make possible – the tangible reality of science – and at a more inchoate level through the use of the language and concepts of science. What it means to be human and the meaning of human life are seen and explained only in terms of scientific constructs. Genetic reductionism and an exclusive focus on sociobiology (our biology explains all that we are and can become with regard to our behaviour) to explain human aspirations and behaviour are two examples of such an approach. The pure science view is intolerant

of the belief that there is a mystery in human existence – which often results in the negation of a sense of wonder – and within its parameters there is no recognized space for spirit.

The proponents of this view are comfortable with the use of reproductive technologies and with euthanasia, seeing most decisions concerning reproduction or one's own death as personal matters involving only individual values and preferences. The gene-machine approach to reproduction is epitomized by a development in Britain. It has been reported that a private clinic was offering women having abortions the option of storing their fetuses in liquid nitrogen so that they may later use a cell from the fetus and the cloning technique that produced the sheep Dolly to create an embryo genetically identical to the aborted fetus. The fetus is not a unique human being but becomes a replaceable object – one that will be reconstructed when it is convenient to do so. The gene-machine approach is also operative, although in a less obvious and dramatic way, in practices that commercialize the human body or human reproduction, such as the buying and selling of human gametes or embryos, or for-profit surrogate motherhood.

The gene-machine approach to euthanasia can be summed up in the words of one Australian politician who, speaking in favour of it, said, 'When we are past our "best-before" or "use-by" date, we should be disposed of as quickly, cheaply, efficiently and painlessly as possible.' This approach equates dying people to stale products in a super-market. The tone of such extreme versions of the gene-machine view can also be captured in the image of human embryos as products in a supermarket.

In contrast, the second view, the 'pure mystery' view, often decries science or is expressly anti-scientific (as can be seen, for example, in the creationists' legal suits against teaching evolutionary biology in schools). This view adopts an intense sanctity-of-life stance, which can be compared to and contrasted with respect or reverence for life, and with respect or reverence for

death. For instance, many people who hold a pure mystery view believe that all medical treatment must be continued until no vestige of life remains. These same people could also have moral difficulties with providing necessary pain-relief treatment that could or would shorten life. Often, this view is derived from fundamentalist religious beliefs. It seeks meaning, and likewise control, through religion. This view does encompass a sense of wonder, but the wonder is not elicited by the new science, which is seen as frightening, at best, and possibly evil.

In her book *The Battle for God*, Karen Armstrong, a leading commentator and teacher on religious affairs, says that the fundamentalist movement is, at least on the surface, an anti-modernist movement; it is based on an intense fear of modernism and is a rejection of it. Because science is associated with modernism, especially in its emphasis on reason to the exclusion of other ways of knowing, we can expect that science would be feared and rejected. Fundamentalists fear modernism because they see it as annihilating them. Armstrong compares and contrasts access to knowledge through *logos* (science) and *mythos* (myths). The fundamentalists are returning to *mythos*, that is, earlier beliefs, but to a very literal interpretation of the myths on which these beliefs were based. People in previous ages realized that these myths were meant to function as ways of access to the psyche, but now these myths and the beliefs to which they give rise are being treated literally. It is not surprising, therefore, that the views of these fundamentalists are incompatible with those based on contemporary science. Armstrong goes on to explain, however, that at a deeper level the fundamentalist movement is essentially a modernizing movement: It is a way in which people who find the modern frightening and threatening can make a transition to the modern. It is important to add here that that transition does not require them to abandon their religious beliefs, but rather will result in their accommodating them in new ways.

The 'science-spirit' view, the third view, seeks a structure to hold both science and the human spirit. For some people, this view is expressed through

religion, but it can be, and possibly for most people is, held independently of being religious, at least in a traditional sense. It recognizes that human life consists of more than its biological component, wondrous as this is. It also involves a sense of mystery – made up of at least the mystery of the unknown or the mystery of the nameless, or both – of which we have a sense through our intuitions, especially our moral intuitions, and accepts that we should respect this mystery. This world view includes a sense of a space for the (human) spirit and of the secular sacred. This view experiences our new science as eliciting wonder at both what we know and, as a result, what we now know that we do not know. It seeks meaning through a combination of science and spirit, which could create a different reality from the other two views.

We can compare and contrast these views. The pure science and pure mystery views represent opposite poles on a spectrum and as a result tend to be two-dimensional or linear. In contrast, the tension created through seeking a combination of science and spirit might create a third dimension – a space for human spirit, one that also fosters our imagination and creativity.

The pure science view operates from a basic presumption of doubt (although an alternative view is that it operates from a presumption of faith in science and that which science reveals, which brings it very close to a religion – or substitute for one, that is, scientism – or an ideology). The pure mystery view operates from a basic presumption of faith in revealed doctrine (revelation). Paradoxically, to the extent that revelation offers an explanation, for instance, of the origin of the universe or the purpose of human life, it could be seen as reducing a sense of mystery. Adherents of both the pure science and the pure mystery views believe that their basic presumption is the only correct one and that the other's view is wrong. It can be argued, however, that the approach taken to forming a world view by the proponents of each of these views is identical, and it is just the content of each view that differs radically from the other. In contrast, the basic presumption

of the science-spirit view is more difficult to identify and the approach taken to forming it differs from that of the other two views. Perhaps it is best described as an openness to all ways of knowing, a comfort with uncertainty, ambiguity and paradox, and the courage to admit that one does not know and to change one's mind. It is a complex, active, constantly changing interweaving of certainty and uncertainty – with the certain open to becoming uncertain, and vice versa. I hasten to add that this is not equivalent to adopting a situational ethics or pure moral relativist approach – that is, the view that nothing is inherently wrong, it all depends on the circumstances. Recognition of unavoidable uncertainty is not incompatible with regarding some things as inherently wrong.

Those who subscribe to the science-spirit view may also be less likely to seek control than adherents of the other two views, probably because this view recognizes that it is less certain; indeed, it has respect for uncertainty and requires us to act in situations that involve uncertainty, under a precautionary ethical principle.

Most importantly, the science-spirit view recognizes that there is more that we *can* do with our new science than what we *ought* to do, so it opens up the debate on what we should and should not do. For instance, under this view, we could regard certain genetic interventions on a human embryo as acceptable (for example, those aimed at therapy for that embryo), but others – for example, those involving alteration of the human germ cell line (the fundamental genetic inheritance that is passed from generation to generation) or human cloning – as inherently wrong. This view would also accept both refusals of treatment and the provision of necessary pain-relief treatment even if it might shorten life, but reject physician-assisted suicide and euthanasia. This view requires the courage to live with the uncertainty that making such distinctions involves.

The science-spirit view recognizes there are many questions we must ask about any given issue, but that there may be no one right answer. Its

fundamental premise is that it is only through an undivided science-spirit approach that it will be possible to tell a collective story – to create a societal-cultural paradigm – of sufficient depth, breadth and width to capture our collective mind, heart and imagination. It will be the greatest challenge of the twenty-first century to realize the potential of this view. That is why we are now searching for ethics, especially in relation to the new science.

References

Armstrong, K. 2000. *The Battle for God.* New York, Alfred Knopf.

Fukuyama, F. 1999. *The Great Disruption: Human nature and the reconstitution of social order.* London, Free Press.

Hein, G. 2000. Interest group litigation and Canadian democracy. *Choices IRPP* (Institute for Research in Public Policy), Vol. 6, No. 2, pp. 3-30.

Katz, Jay. 1984. *The Silent World of Doctor and Patient.* New York, Free Press.

Saul, John Ralston. 1995. *The Unconscious Civilization.* Concord, Ont., Anansi.

Singer, P. 1990. Animal Liberation, rev. ed. New York, Avon Books.

Somerville, M. A. 1992. Law as an 'art form' reflecting AIDS: A challenge to the province and function of law. *Fluid Exchanges: Artists and Critics in the AIDS Crisis*, Miller, J. (ed.). Toronto, University of Toronto Press, pp. 287-304.

_____. 1992. Messages from three contemporary images of medicine: Failed medicine, miracle medicine and science fiction medicine. *From the Twilight of Probability: Ethics and politics*, Shea, W. R. and Spadafora, A. (eds). Cambridge, Mass., Science History Publications, pp. 91-105.

_____. 1995. Planet as patient. *Journal of Ecosystem Health*, Vol. 1, pp. 61-71.

Wright, R. 1994. *The Moral Animal: Evolutionary psychology and everyday life.* New York, Pantheon Books.

Yankelovich, D. 1996. Trends in American Cultural Values. *Criterion*, August, pp. 2-9.

Chapter 3

Margaret A. Somerville

The Ethics of Immortalizing Our Genetic Selves

The ethics of human cloning has been on the public agenda since the birth of Dolly, the cloned sheep. Cloning techniques make possible both the creation of genetically identical human beings and of tissues, organs or cell lines (a homogeneous group of cells derived from a single sample of cells from a tissue or organ) that are genetically the same as the donor. We can clone higher animals and, therefore, in all probability will be able to clone humans. Human cloning can be undertaken for two reasons: to produce children who are genetically identical to the cell donor (*human reproductive cloning*), or to produce embryos for research or to manufacture therapeutic products, including tissues or organs for transplantation (*human therapeutic cloning*).

Our ethical reaction to the new genetic technologies often starts with what philosopher and ethicist Professor Arthur Schaefer of the University of Manitoba has called an ethical 'yuck factor'. Many people had such a reaction to the possibility of human cloning. But as our familiarity with these new technologies

* Adapted from Chapter 3 of *The Ethical Canary: Science, society and the human spirit*. Somerville, M. A. 2000. Toronto, Canada, Viking.

increases and our dread decreases, we may move from ethical rejection and horror to ethical neutrality and ethical acceptance – usually with safeguards – and finally to positive approval of the new technology, especially if we see it as offering major benefits.

This slippery slope to acceptance of ideas we once viewed with disgust starts with familiarity and overcoming dread, factors that can be linked with moral intuition. Therefore, we need to be careful in allowing these changes to occur and not to suppress our moral intuition; we may have to consciously prevent familiarity and the loss of dread regarding scientific developments from dulling our ethical intuitions about these discoveries. And since these intuitions are often manifested as a sense of anxiety, we should not ignore this anxiety.

But some eminent scientists do not agree. They see such anxiety as pathological. They understand the world and human life through science only. They espouse a gene-machine or pure science view of human life and a world view based on it. They do not respect ways of knowing other than reason (although scientific discovery depends on these other ways, especially on creativity, imagination and intuition). Moreover, these scientists tend not to see science's profound impact on our metaphysical reality, especially its human spirit dimension. Indeed, most do not even recognize that this reality exists or, if they do, that it can be damaged. As sociologist Professor Howard Kaye says, the nearest they come to acknowledging the potential for damage is when they admit that the new science raises 'reasonable concerns about potential psychological and social harm'. They believe, however, that these concerns are counterbalanced by other values supporting individual choice and freedom of scientific enquiry and 'the good' that they see their science as being capable of delivering.

These scientists regard people who oppose human cloning as doing so on the basis of 'deep cultural prejudice' – to use the words of Professor Richard

Lewontin, professor of zoology at Harvard University – and sheer ignorance of biology. They believe, as Kaye reports, that 'the fear that human cloning may prove dehumanizing and therefore ought to be banned is simply the hysterical reaction of the modern-day "Luddites" held in thrall by "ancient theological scruples" which must be swept aside so that scientific progress and human liberation may proceed.' In other words, they believe that any opposition to their science is largely based on ignorance rather than insight. Consequently, they see the solution to this opposition as better science education.

These scientists would accept, for instance, a short-term ban in order to have time to correct 'public misconceptions' about the science and to minimize safety risks, which they see as the only real concern. They see voluntary moratoriums on human cloning as the least threatening way to accommodate what they regard as unreasonable fears on the part of the public. They bolster their approach with statements that the public's fears are based on science fiction and with long litanies of the good that will result from the technology, such as providing infertile couples with children, or saving dying children through the transplantation of tissues or organs.

These scientists dismiss the public's widespread moral intuitions against human cloning. Kaye describes this dismissal as blocking moral judgement and the public's moral opposition. He makes the very important point that

> apprehensions [on the part of the public] so nearly universal in expression – that cloning constitutes a threat to the dignity and sanctity of human life – ought not to be dismissed so cavalierly. ... The claim of cloning's supporters, that the anxieties experienced [by the public] may be safely ignored because they will soon diminish as they always have done before, is ... profoundly misguided. These anxieties may indeed diminish as panic gives way to temptation or fatalism, but the price of such accommodation may seriously reduce our worth as human beings.

Kaye also argues that the scenarios the public construct of the mad scientist who will use cloning or the multiple clones of

the mad dictator may indeed be 'misconceptions of science but the dangers which they sense so viscerally may be very real indeed'. In other words, our anxieties may be needed to guide our moral responses to this science. It is not enough simply to look at the consequences of our actions, we also need 'clarity about the ultimate meaning of our actions'.

Moreover, we must ensure, as health lawyer and ethicist Professor George Annas warns, that individual scientists do not 'act first and consider the human consequences later'. In human cloning, society faces the necessity to make moral choices and other important decisions without having had actual experience with this technology and despite a lack of knowledge regarding at least some of its risks. Making these decisions must, therefore, call upon the 'other' ways of knowing: intuition, common sense, human memory (history), ethics, imagination and creativity, and 'examined emotions', and not just reason as the scientists who want to carry out human cloning propose.

So keeping in mind the general scene just described, in which the human cloning debate is taking place, what are the facts? What is involved in human cloning? In this area, in particular, good ethics depend upon good facts.

How are clones created? We could clone humans who have already been born, human embryos, or organs, tissues or cells. Even these latter types of cloning can involve human embryos. Human cloning involving embryos could occur in three ways: through the transfer of the nucleus of an adult cell into an enucleated human ovum (the 'Dolly technique', *somatic cell nuclear transfer* [SCNT]) to create an embryo; through embryo splitting, which occurs naturally with identical twins, triplets or quadruplets, but which can also be undertaken in the laboratory with embryos that would not have divided naturally; and through cloning from human embryo stem cells (primordial cells capable of forming any part of the human body) taken from embryos. Sometimes, all three procedures are

grouped together and referred to collectively as human cloning. There are, however, differences among them, some of which are ethically relevant. The first two methods can result in an identical person; in the last, only organs or tissues genetically identical to the donor of the stem cell can do so. In the latter two methods, the clones are genetically identical; in the first, the clone's mitochondrial DNA, which comes from the donor of the enucleated ovum, differs from that of the person who donated the somatic cell (a cell that is not a reproductive cell, that is, not a gamete – an ovum or a sperm).

The Dolly technique involves taking an ovum (an egg) and removing its nucleus with the DNA (the genes) that it contains – the ovum is then empty except for the mitochondrial DNA in the cytoplasm (the liquid) of the ovum. (The mitochondrial DNA is passed through the maternal line from generation to generation unchanged, it was thought, except by mutation. But some very recent research indicates that sperm might have an effect on it.) Then a somatic cell is taken from the person who is to be cloned. Every cell of our bodies contains all our genes. The genes from this somatic cell are placed into the enucleated ovum. This new cell is then treated in such a way that it starts to function as a human embryo. It will be the clone of the donor of the somatic cell.

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Human cloning can be undertaken for one or other of two purposes. The goal of human *reproductive* cloning is to produce a child. Human *therapeutic* cloning involves producing embryo clones through either the Dolly technique or embryo splitting, then using either the embryos or stem cells from the resulting embryos as 'living human tissue generators' or for other research purposes. These stem cells can also be cloned.

What are the facts about human embryonic cells? The cells of the very early embryo are totipotential, that is, they have the potential to function as another human embryo and can each give rise to an entire new being. They are also pluripotential,

that is, they can be manipulated to produce any tissue or organ. Although every cell in our body contains all of our genes, at an early stage, the genes in each cell differentiate so that, for example, our liver cells express only the liver genes they contain, or our skin, only the skin genes – the other genes in the liver or skin cells remain silent. After differentiation, a cell can form only the tissues or organs for which it has been differentiated – unless it is de-differentiated using the Dolly technique.

Human embryonic stem cells are taken from a human embryo at about the one hundred-cell stage. They are no longer totipotential but are still pluripotential, that is, they can be caused to differentiate into a certain tissue or organ. Taking stem cells from an embryo necessarily destroys it.

To summarize: Up until a certain stage, each cell of a human embryo can form another embryo; every embryo forms stem cells within it; taking stem cells from an embryo destroys the embryo; stem cells cannot function as an embryo; and stem cells can be cloned.

We must ask: What is the moral status of a human embryo, of embryos cloned from another embryo, and of human embryonic stem cells collected in the way described? Some people believe that the human embryo has full human moral status, others that it has special moral status, and a few that it has no moral status.

Those who believe that it has *full human moral status* argue that, from its earliest beginnings, all human life deserves the same respect. Therefore, they believe that we must not undertake any research that is not intended as necessary therapy for the embryo on which it is carried out. The embryo is *human life with potential* as we all are until we die.

People who believe that the human embryo has *special moral status* as the earliest form of human life, but not (yet) the same status as the rest of us, would allow human embryo research under certain conditions. They

would prohibit creating human embryos just to carry out research on them and would permit it only on 'spare embryos', those left over from *in vitro* fertilization procedures. And they would limit research on human embryos to the first fourteen days of cell division after fertilization. These people reject the view that it is inherently wrong to carry out research on human embryos, but seem to accept that it is inherently wrong to create them for this purpose – to do so shows a basic disrespect for human life. They might also be objecting to the creation of embryos just for human use or simply as a research tool because to do so harms important values and symbolism attached to human life, especially the most vulnerable forms of human life, of which embryos are a prime example.

Other people believe that it is morally acceptable to create human embryos for research purposes. They usually justify their stance on the grounds that while human embryos are of human origin and, as such, have special moral status and deserve respect, this status does not prohibit research on them. They point out that the embryo is not a conscious being who can suffer pain and that great good could come from the research. They see human embryos as *potential human life*.

Those who do not believe that the human embryo has any special moral status would create and use them for research as they would any other tissue of human origin. This view was forcefully presented by molecular and evolutionary biologist Professor Lee Silver of Princeton University at a conference I attended in Squaw Valley, California. I had given a presentation outlining the case against human cloning, and in the course of this talk, I argued for recognizing the moral status of the human embryo. Professor Silver followed me as a speaker to present the case for human cloning and embryo research. He stood before the audience, melodramatically took out a tissue and blew his nose into it. Without saying anything, he held it up to the audience, who were watching him attentively. He then said, 'This tissue has cells on it from the inside of my nose. I would like Margo

Somerville to understand that I believe that these cells have the same moral status as human embryos.'

To summarize: When we disagree on the moral status of human embryos, we disagree on the ethics of human embryo research. Human cloning necessarily involves research on human embryos. Therefore, the different views on the moral status of human embryos and human embryo research translate into different attitudes about the ethics of human cloning, quite apart from any other factors that might cause us to differ in our views on the ethics of cloning. We should keep in mind that our approach to human cloning, embryo research, abortion, and the use of fetuses in research or as a source of organs or tissues for transplantation are all intimately connected.

We can test the inherent wrongness of human cloning from a secular base by asking two questions related to the two fundamental principles that I suggested previously should guide our decisions about ethics: Does human cloning contravene respect for human life? And would carrying out such cloning damage our sense of the human spirit – by which, as I explained in Chapter 2, I mean the essential, intangible, invisible, unmeasurable reality we need to live fully human lives, that 'non-physical entity' through which we find a sense of meaning in our lives? If it does either, it is inherently wrong.

Insights about what respect for human life and the human spirit requires in relation to human cloning can come from diverse sources. For instance, Kaye bases his stance against human reproductive cloning on concepts articulated by Emile Durkheim in his book *Suicide*. Durkheim refers to the belief in the inherent dignity and worth of human life as 'the religion of humanity' and concludes that it is the only cohesive bond in a diverse and secular world. He regards this belief as the last one that 'unites us as a human community and serves as the essential basis of our social and moral order'. The famous French philosopher Paul Ricœur sums up the same approach in a few simple but powerful words: Something is owed to human beings

simply because they are human. This religion of humanity is almost certainly the non-negotiable minimum without which we cannot form a viable human society – or at least not one in which most of us would think it was worthwhile living. It requires that we have respect for each individual human life and human life in general, and, I propose, for the essence of human life, itself (the human germ cell line), and the transmission of human life. Human cloning challenges us on all of these bases.

However, even if we were all to agree that we must have respect for human life in all these senses, we are likely to disagree as to what should be allowed and disallowed if we are to maintain such respect. In particular, we will disagree whether human cloning – reproductive or therapeutic – is inherently disrespectful of human life. For instance, what does respect for human genetic diversity require and does human cloning breach these requirements?

As a society – indeed, as a global community – we must respect the integrity of the human gene pool, which we hold in trust for future generations. Because of our new scientific powers to intervene and change this gene pool, we are faced with decisions no other people have ever confronted. Many people believe that we must not interfere with the human gene pool – or, at the very least, not wrongfully interfere with it – because it is the common heritage of humankind and it would be wrong for us to change that heritage. Such a view reflects a secular-sacred approach to the human gene pool. Just from the perspective of practical survival, genetic diversity is important to ensure the integrity and resilience of the human gene pool and, therefore, of human life. Some people might respond that we would never be able to reduce its diversity to the extent that it would matter in this regard. But even if that is true, genetic diversity is also important for individuals. It is an amazing thought that for every person who has ever lived (genetically identical sibs aside), there has never in the past been anyone genetically identical to that person and never will be in the future unless the person is cloned. This genetic uniqueness

is also important in relation to upholding the societal value of respect for persons: It helps to prevent us from regarding individuals as replaceable commodities and losing respect for people, in general, in doing so.

If we decided that human cloning is inherently wrong, it would mean that cloning must not be undertaken no matter how beneficial the consequences of using it could be. Prohibiting a procedure that could be the only hope of saving life or avoiding horrible suffering, or that could help people to have a child and that some do not regard as wrong, can be seen as breaching norms of both compassion and tolerance. These are some of the many forces that indicate it will be difficult to find a strong consensus that we should prohibit human cloning and, if we were to achieve this agreement, to enforce such a prohibition. Let's look at some of these arguments, starting with intense individualism.

Intense individualism is one of the powerful, current trends that favour a situational ethics approach to human cloning. Intense individualism encourages us to focus on individuals' rights to autonomy and self-determination, with societal interests – the common good – if considered at all, taking a subordinate place. Infertile people who want to have their 'own' genetically related child can make powerful emotional arguments that they should not be prevented from doing so through cloning. Likewise, desperately ill people or those with diseases that cause great suffering, such as Alzheimer's or Parkinson's, can make it extraordinarily difficult to argue against human therapeutic cloning – to argue that it is inherently wrong – when it could offer them chances of treatment or even cure.

The predominance of intense individualism has given rise to a concern that, as a result, we have lost a sense of community. In the last few years, another concern has been added to this, that we have also lost a sense of the common good. For instance, philosopher and ethicist Dr Daniel Callahan criticized the United States National Bioethics Advisory Commission's report

on human cloning precisely on the grounds that the report focused only on risks to individuals and failed to take into account the requirements of protection and promotion of the common good and the harmful impact that allowing human cloning would have on the common good. The commission proposed placing a moratorium on human reproductive cloning, not a permanent prohibition of it. Callahan believes that this recommendation shows a failure to understand what is needed to protect the common good.

Some versions of *reproductive rights* also favour reproductive cloning. The proponents of these rights claim that reproduction is a private matter involving only individuals and their choices, and these choices must not be interfered with by others. Cloning can be seen as simply another reproductive choice that can be justified by the free and fully informed consent of the person who wants to be cloned. (Although the clone's consent is not obtained, of course.) The basic philosophy behind the doctrine of informed consent is respect for people's rights to autonomy and self-determination. Provided, therefore, that people understand what they are doing – especially the risks involved – they should, as far as possible, the argument goes, be allowed to do what they want. This approach means that consent functions as not only a necessary safeguard, but also as a sufficient one. It maximizes individual liberty, even when this is at the expense of other values.

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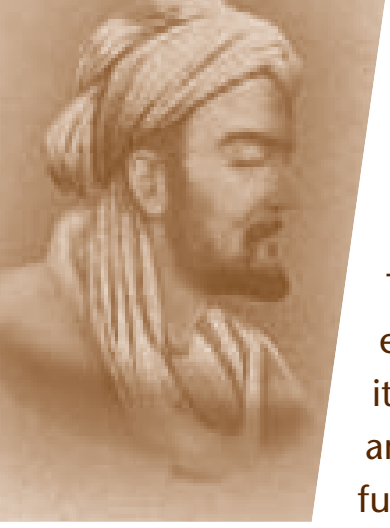
In making choices about whether to prohibit certain reproductive technologies such as human cloning, we need to keep in mind that we are facing the technological imperative – that is, 'have technology, must use it' – in one of its most dangerous forms. I suggest that the most appropriate comparison is with the discovery of nuclear fission and the development of the atomic bomb. In a 1947 speech given at MIT, T. Robert Oppenheimer, one of the scientists who developed the atomic bombs that were dropped on Hiroshima and Nagasaki, said, 'In some sort of crude sense which no vulgarity, no humour, no overstatement



can quite extinguish, the physicists have known sin; this is a knowledge which they cannot lose.'

This statement raises the question: 'Could we gain important ethical insights about human cloning by considering whether it is evil?' Professor Upendra Baxi, a distinguished Indian jurist and human rights activist, developed a concept he calls the functionalization of evil, and it is relevant to this enquiry. Baxi argues that one of the dangers in our present world is that we have lost a sense of evil and that, in part, this has occurred because when evil happens we tend to focus only on the good that comes out of it and, in the process, lose a sense of the evil that was involved. We may be in danger of doing this in relation to human cloning. If it is intrinsically morally wrong to clone humans, whether for therapeutic or reproductive purposes, we must somehow maintain a sense that it would be evil to do so, no matter how much good could come out of it.

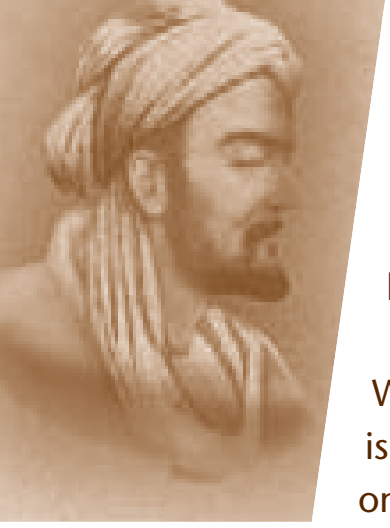
In two other respects, Oppenheimer's statement also merits thorough consideration in relation to both forms of human cloning: First, is it correct that, as scientists have traditionally argued, science is value-free and that we should never place restrictions on the discovery of knowledge? And, second, can we foresee the harm human cloning would cause and, even if we could, could we control it?

The idea that science is *value-free*, that there is an *absolute right to freedom* of scientific enquiry and it is wrong to restrict scientific research, leads to a conclusion that research on human cloning should not be inhibited. The traditional view that science itself is value-free has been increasingly challenged in the last few years and, as a result, is now largely abandoned. That is especially true in the context of the life sciences, because of the possibility that they could become the death sciences if they were to be used in the cause of bioterrorism. More and more people believe that if scientists can see that immense harm would result from their discoveries, they have ethical obligations not to pursue them. For instance, biological

warfare research can be regarded as inherently wrong and therefore it must not be undertaken. But not everyone agrees. They argue that science is value-neutral, and it is only when we apply it that ethics comes into play. Scientists are often concerned that ethics will inhibit them in pursuing scientific knowledge, and the split between so-called pure and applied science has been used to avoid ethics being applied to pure science. But ethics must be embedded in science at all stages of discovery and development. When we see the mind- and world-altering power of the scientific discoveries of just the last ten years, it should be piercingly clear that we cannot afford to have ethics simply as an add-on or afterthought. Power entails responsibility, requiring that we embed ethics in every aspect of science. To give just one example of value-laden pure science, using human embryos as research material or making human-animal hybrids to carry out research on them is not a value-neutral activity and must be governed by ethics.

A common argument also put forward is that there is no point in trying to 'stop' new and controversial techniques, such as human cloning, because they will go forward regardless of whether they are regarded as ethically acceptable (unless, of course, everyone considered them to be ethically unacceptable and personally refrained from using them). If this view is correct, it reflects our society's moral or ethical bankruptcy – which it is deeply disturbing to think might have occurred. Moreover, just because human cloning is inevitable and uncontrollable does not mean that we should not try to stop it if we believe it is ethically wrong, any more than, as Annas says, 'a recognition that controlling terrorism or biological weapons is difficult and uncertain, [does not justify] ... making no attempt at control.'

A useful analogy to law can be made here. The vast majority of people do obey the law: If they did not, the law would be ineffective. The same is true for ethical rules. Consequently, the fact that some people do not comply with them, as indeed some people do not comply with the law, should not make



us despair of the effectiveness of these rules or disregard the necessity for them. Moreover, as is true with law, we usually notice only where ethical requirements are not effective, not the harms they prevent.

We should also be careful that this 'impossible-to-stop' argument is not simply one way to argue against placing any restrictions on scientific research. A particular aspect of this argument is encountered when corporations invest very large amounts of money in scientific research, such as human cloning, that raises major ethical problems. This investment creates pressure not to restrict – and certainly not to abandon – the research, even when restriction or abandonment is ethically required. Further complications and difficulties in this regard are generated by the intertwining of universities, industry and government in the research enterprise. This intertwining can result in a situation in which no institution is free of conflict of interest and can ensure that what is done is ethical. In short, ethics is captured by the research enterprise.

Finally, another factor favouring human cloning is that it offers more than the usual *promise of some sort of temporal immortality* – that of one's genome – and, even more so than natural reproduction, of genetic immortality. This promise might be important to some people who no longer believe in the supernatural.

I am not sure we will ever agree as a society that there is a 'right' answer about the ethics of human cloning – certainly of therapeutic cloning, although we might agree to prohibit reproductive cloning. The problem is, to return to a previous theme, that for many people the risks and harms they take into account in deciding whether they are ethically justified in running or imposing risks and harms do not extend to damage to our most important human values and our sense of the meaning of human life. Moreover, even were we to agree on what we *should* do ethically, would we actually follow that course?

Human therapeutic cloning

Let's turn now to consider the ethics of human therapeutic cloning more specifically. Both human embryos and embryonic stem cells can be cloned – that is, multiple copies can be made. Questions this raises include these: If one believes that it is ethically acceptable to use spare embryos for research, is it acceptable to make multiple embryos, as long as one starts with a spare embryo? Do prohibitions or restrictions on embryo research apply to the use of embryonic stem cells? Does the source of the stem cell matter and, even if it does, does it matter once the cell has been isolated? For example, if we believe that it is not ethically acceptable to create human embryos from gametes taken from aborted fetuses, is it ethically acceptable to use a cloned cell line developed from such a human embryo? Or, if we believe that abortion is ethically unacceptable, is it ethically acceptable to collect stem cells from aborted fetuses for use in human therapeutic cloning or to use cells cloned from these stem cells? If we have ethical reservations about abortion, does this mean that research using stem cells derived from an aborted fetus is not ethically acceptable? Morally, can we separate these cells from their origin in abortion?

Is human therapeutic cloning inherently wrong? And, if not, or if we use just a situational ethics approach, is it ethically acceptable?

If using human embryos for therapeutic cloning is inherently wrong, we must not do it, no matter how much good could be achieved. The extraordinary medical benefits that could result would not be a justification for the use of human embryos. To use human embryos just as an instrument for doing good for the rest of us damages respect for both human life and the reality that constitutes the human spirit. We cannot regard a human embryo as wondrous and use it simply as an object on which to carry out research that is not intended to benefit it or to provide it with a chance of life. We lose our sense of wonder and awe at our ethical peril. These senses are very easy to

damage, especially if we use our new science in certain ways, and the loss and damage we cause to our metaphysical reality may well be irreversible. The use of just one embryo for human therapeutic cloning presents risks to respect for life and for the human spirit and can harm them.

In the same way, creating multiple embryos from the same embryo damages respect for human life itself – even if it does not contravene respect for any one human individual – and for the transmission of human life. It turns a genetically unique living being of human origin into just an object and one that is replicable in multiple copies. It changes the transmission of human life from a mystery to a manufacturing process. It fails to recognize that we are not free to treat life in any way we see fit, that we do not own life. Rather, we have life and, most importantly, life has us. Recognizing that we owe obligations to life can provide a basis on which to establish respect for life in a secular society. This recognition means that we must ask, 'What must we not do because to do it would contravene respect for human life itself?' I believe that one answer to this question is the creation or use of human embryos for human therapeutic cloning. This cloning can, therefore, be regarded as inherently wrong. In summary, I propose that, even leaving aside any questions of the abuse of human therapeutic cloning, the intentional creation and destruction of human embryos it involves could seriously damage important values and the 'ethical tone' of our society.

An alternative analysis for those who reject a concept of inherent wrongness is one based on situational ethics: Nothing is inherently wrong – it all depends on the circumstances. Under this approach, in contrast to one based on inherent wrongness, 'doing good' through human therapeutic cloning can be a justification for the unavoidable harm to embryos that it involves – and possibly for the harm that it does to respect for human life and the human spirit. Most people who regard human therapeutic cloning as ethically acceptable do not consider these latter harms to be

present, however, in the human embryo research that human therapeutic cloning necessarily involves. Could the reason be that to raise such concerns would give them validity and, as a consequence, make it difficult to argue that human embryo research is ethically acceptable? The good focused on in justifying human embryo research and therapeutic cloning includes producing organs and tissues for transplantation, repairing severed nerves, or treating cancer, diabetes, multiple sclerosis, Parkinson's disease, Alzheimer's disease or genetic disorders. It is very hard, and will take great courage, to refuse such extraordinary benefits.

One reason – a paradoxical one – that it is difficult to ensure that the new science is ethically acceptable is that it has the potential to do so much good. There is an old saying in human rights that nowhere are human rights more threatened than when we act purporting to do good. When we focus on the good that we are setting out to achieve, we can be blind to the dangers, risks and harms involved, including ethical harms. This is probably a companion phenomenon to the functionalization of evil, discussed previously.

But could human therapeutic cloning also be considered unethical under a situational ethics approach? To respond requires identifying the harms of this cloning and balancing them against the benefits. (We should keep in mind that we will not necessarily agree on what counts as benefits and harms, and how to weigh them when they conflict, because these decisions are value judgements.)

First, among the harms is the fact that human therapeutic cloning makes human reproductive cloning more likely and more difficult to effectively prohibit – it opens up a slippery slope. But this argument holds only if we believe that human reproductive cloning should not be undertaken. I discuss this issue in the next section. Second, human therapeutic cloning (like human reproductive cloning) opens up the possibilities of genetic enhancement and disenhancement through alteration of the human germ-cell line – the units of heredity passed on from

generation to generation. If we believe that these types of intervention are wrong, we may not want to make them easier to achieve. Third, even if we do not regard using human embryos for research as showing disrespect for individual human life, it can show disrespect for human life in general. For example, embryos used in therapeutic cloning have been described, as mentioned previously, as 'living human tissue generators' or, in stark language, a human-embryo manufacturing plant.

Fourth, therapeutic cloning (again, like reproductive cloning) also shows disrespect for the transmission of human life and could affect our sense of wonder about it. Film critic Len Blum, writing about Stanley Kubrick's film *Eyes Wide Shut*, says in relation to the sexual intimacy portrayed in that film: 'Because I believed the events were real, I savoured every moment. One isn't aroused – one is sexualized. Made conscious of sexuality. And since sexuality is the transmitter of human life, the feeling was akin to becoming more conscious of life itself.' What would it mean to some of our most profound human experiences if we could not only transmit human life asexually, but also do so for the purposes of setting up a basic manufacturing process based on this life? Blum's words should warn us that what we would lose is highly subtle and nuanced, but extraordinarily important. The sexual transmission of human life is integral to our sense, as both individuals and a society, of ourselves and of the meaning of human life. Can we afford asexual transmission, no matter what benefits it promises? Human life is not a commodity. Can we ever afford to make it such?

Ethicists Professor Glenn McGee and Professor Arthur Caplan present a very sophisticated argument in favour of human embryo stem cell research, which always involves the destruction of embryos to obtain the stem cells. The same considerations apply to the use of human embryos in therapeutic cloning. They propose that the central ethical question revolves around whether use of the embryo is an acceptable 'moral sacrifice' of human life. They point out that the moral imperative of

compassion motivates this stem cell research. (In this way, they distinguish it from abortion carried out for superficial reasons.) They assume, for the purposes of argument, that the one hundred-cell human blastocyst from which the stem cells are taken is a 'fully human person'. They conclude that its only unique characteristic is the recombinant DNA from both parents that it contains. They point out that this DNA will survive through the creation of cell lines using the pluripotent stem cells derived from the embryo. This DNA could later be used to make a 'new nuclear-transfer-derived embryo' (that is, a 'replacement' embryo could be created using the Dolly technique) that would have identical DNA to the original embryo. In essence, they are arguing that the destruction of the 'original' embryo to obtain stem cells is not necessarily the destruction of the only unique feature of that embryo, which is its DNA, and that this is an answer to those who oppose embryo stem cell research on the grounds that it involves the destruction of human embryos. In other words, they value the genetic uniqueness of the embryo more than the embryo itself, and provided the former can be preserved the latter may be destroyed. (This is a similar approach to that mentioned in Chapter 2, of cloning an embryo from an aborted fetus in order to have the 'same' baby at a later date.) They point out that of the needs that merit sacrifice, reducing widespread suffering from disease – the goal of human embryo stem cell research – is an obvious and compelling one.

McGee and Caplan's argument for the use of embryos is constructed in such a way that it would not apply to more developed forms of human life. Those forms that can experience pain or have memory should not be sacrificed for the benefit of others because features such as memory – unlike the unique DNA – are not replaceable. Their argument is an example of sophisticated science being used as a solution to ethical problems raised by sophisticated science. It is a situational ethics approach, but much subtler than most of them and borders on asking whether using embryos as the source of stem cells is inherently wrong. The focus of their enquiry in this latter respect is not on whether it is inherently

wrong to intentionally destroy an early human life; rather, it is on whether it is inherently wrong to destroy such a human life if all the unique features of this life can be replicated at a later time. This approach is a highly imaginative combination of philosophy, semantics and avant-garde science. But in using it, would we just be defining away the real ethical issue – namely, are we justified in intentionally destroying a human embryo, in using it as an object to benefit the rest of us?

There may be some answers to the ethical problems raised by human therapeutic cloning on which there could be consensus. With further scientific advances, we might not need to use an embryo to obtain stem cells but could obtain them from the person who needs a tissue or organ or from another person. It might also eventually be possible to cause a somatic cell taken from the person who needs a transplant to de-differentiate and re-differentiate into the tissue or organ that is needed without the creation of an embryo. The problem is that developing this science will take time. Usually doing science in 'ethics time' means that we need time to work out the ethics that should govern the science. But here, somewhat ironically, we need time to work out the science in order to avoid ethical problems.

We need thorough consideration of the competing interests that are brought into play by human therapeutic cloning. These are, on the one hand, that we cannot wait for further scientific advances, because those who are suffering or dying and could be helped by human therapeutic cloning and embryonic stem cell research need treatment now. On the other hand, we will not be able to repair or reverse the harm that we would do to our sense of respect for both human life and its transmission, and of wonder about them, if we unethically use human embryos.

On a personal note, even though I believe that human cloning is morally wrong, I am not sure, if my life or that of someone I loved depended on using therapies developed as a result of human therapeutic cloning, that

I would make the decision I believe is the ethically correct one. We should be very concerned that the cynics might prove to be correct, that no matter what ethical conclusions we come to, human cloning will proceed, especially if people believe that the good that might come from this new science would far outweigh any of the risks or harms we currently perceive it as presenting.

Human reproductive cloning

I want to turn now to human reproductive cloning – using cloning technology with the goal of creating genetically identical people. Some of the same ethical issues are raised in all cases of human cloning, whether reproductive or therapeutic – for instance, the ethics of creating human embryos through cloning and carrying out research on them. Indeed, undertaking cloning is, in itself, research. But reproductive cloning also raises different issues and, while some people would prohibit both forms of cloning and others permit both, some people would allow human therapeutic cloning but prohibit human reproductive cloning – in particular, the use of the Dolly technique to clone a baby from an adult human.

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A strong argument against creating such clones is that they would be deprived of their unique genetic identity, in a way that is not true even of naturally occurring genetically identical siblings, and to do this is to wrong them. The philosopher Hans Jonas argues that respect for the human person requires respect for human genetic diversity, and this is why human reproductive cloning is inherently wrong. On the basis of Jonas's work, and quoting the philosopher, Annas constructs a powerful argument

that cloning is always a crime against the clone, the crime of depriving the clone of his or her 'existential right to certain subjective terms of being' – particularly, the 'right of ignorance' of facts about his or her origin that are likely to be 'paralyzing for the spontaneity of becoming himself' or herself. This advance knowledge of what another has or has not accomplished with the clone's genome

destroys the clone's 'condition for authentic growth' in seeking to answer the fundamental question of all beings, 'Who am I?'

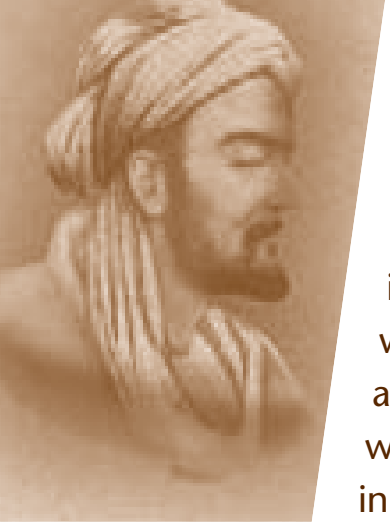
Jonas says if we are to act ethically we must never 'violate the right to that ignorance which is a condition of authentic action. ... The ethical command [is] ... *to respect the right of each human life to find its own way and be a surprise to itself.*' Annas concludes in a similar vein that 'through human cloning we will lose something vital to our humanity, the uniqueness and, therefore, the value and dignity of every human. Cloning represents the height of genetic reductionism and genetic determinism.'

One of the paradoxes in the debate on human reproductive cloning arises in relation to whether genetic difference matters. In Chapter 2, I discussed the gene-machine view of the human person. Those who adopt this view, particularly the scientists, are relying on a 'Genes-R-Us' concept – or, as sociologists Dorothy Nelkin and Susan Lindee describe it, a view that DNA has become the human soul, that is, a DNA mystique. And yet, at the same time, in order to justify human reproductive cloning, these same people argue that creating a child without a unique genetic identity should not be viewed as a problem. They often point out that genes are only partly responsible for who we are. For example, some scientists who do not want to be prohibited from undertaking human reproductive cloning have been identifying and emphasizing the differences between each of the members of two sets of naturally conceived identical quadruplets who live in the United States. Alternatively, or in addition, they argue that in human cloning carried out through somatic cell nuclear transfer (the 'Dolly technique'), the small genetic difference between the person from whom the cell was taken and the clone – as explained above, the clone has mitochondrial DNA different from that of the cell donor – is sufficient to constitute genetic difference to the extent that this should matter. But let's face it, most people who want to have a child cloned from their DNA choose to do so because they want a genetically related child – and some specifically want a genetically identical child. These people are proposing

that genes both matter and do not matter, and the position they take in any given circumstances depends on the argument that needs to be won.

An argument against human reproductive cloning – one related to that based on a loss of genetic diversity – is that each person has a right to a *unique genetic identity*. Indeed, it has been proposed by Annas that 'the central problem of cloning [is] the devaluing of persons by depriving them of their uniqueness'. Again, an argument to the contrary is that we already have naturally occurring identical twins, triplets or even quadruplets, and we do not regard their lives as of less value or less worthy of respect because they are not genetically unique. Why then is this a problem with human cloning? With the advent of cloning technology, these naturally occurring siblings are sometimes referred to as natural clones. Therefore, the argument goes, we are just using technology to do what can occur naturally. However, there are important ethically relevant differences between situations of naturally occurring and artificially created genetically identical people. These include that a different moral order (different ethical concerns and obligations) is involved when we intentionally create such a situation: When we intervene on others, we have moral responsibilities that we do not have if the same situation occurs naturally. Naturally occurring identical sibs are also of the same age and, therefore, their life is, as Jonas says, 'a surprise to each of them'. And moreover, even if human reproductive cloning's contravention of genetic uniqueness was not a major ethical concern, it is not the only reason that such cloning is wrong.

The further question this discussion raises is whether embryo splitting with the intention of producing identical siblings to be born contemporaneously is also wrong. In my view, it is. Although this situation could occur naturally, the intervention of a human actor who intends to and does cause this result makes it ethically unacceptable. It is human cloning in a sense in which naturally occurring genetically identical human sibs is not: It is cloning of a human by a human.



We can also argue that human reproductive cloning is inherently wrong because as a general rule each of us has a right to be begotten by chance as far as our genetic inheritance is concerned, not by human choice. This objection would encompass an argument that we have a right not to have another person design us in his or her image, which is precisely what human reproductive cloning involves; it is 'playing God' in the most fundamental sense (in the sense that, as the Bible states, God created man [sic] in His image, and we are producing clones in our image) and in a way that other interferences with or manipulation of human reproduction are not. We have a right to come into existence through human reproduction, not, as is the case with human cloning, through replication. One variation on the argument that undertaking human cloning is 'playing God' I found very surprising. This approach, suggested to me by a geneticist who favours human cloning, is that deeply religious people believe that God intended them to be His co-creators. Therefore, they can also believe, he said, that God intended people to discover the science of genetic manipulation, including cloning, and to use it to take over more of His creative work.

There must be reverence for the creative forces of nature in the passing on of human life and we need to enquire what limits this requirement would place on us in using our genetic science. Human reproductive cloning – and human therapeutic cloning – contravene the most fundamental requirements of reverence in the passing on of human life.

Concepts such as dignity are relevant in assessing whether human reproductive cloning contravenes requirements of respect for human beings and human life and, therefore, is inherently wrong. But whether humans are seen to have intrinsic dignity (dignity simply because they are human) or extrinsic dignity (dignity attributed to them by other people) will influence how we would view human reproductive cloning. A concept of intrinsic dignity is more likely to result in a conclusion that human reproductive cloning is inherently wrong than is one of extrinsic dignity.

A concept of extrinsic dignity makes it easier to argue that whether human reproductive cloning is an affront to respect for human dignity simply depends on how we view the cloning process and whether we attribute dignity to the resulting clone. A concept of intrinsic dignity is much less open and flexible in this respect. To explore what respect for intrinsic human dignity would require in the context of human cloning, we can rephrase Ricœur's principle: What do we owe to the human beings who would result from cloning – in particular, what does respect for their human dignity require that we not do to them – simply because they are human? Since all humans must be seen as subjects, not objects, we must avoid using technologies in any way that detracts from their being treated or seen as a subject. The obligations we owe to human beings include not to manufacture them; not to make them into objects, things or commodities; and to respect their right not to be designed by another human. Rather, we must allow each person his or her individual and unique ticket in the great genetic lottery of the passing on of human life. Human reproductive cloning contravenes all of these requirements.

This view – that we have a right to come into existence through genetic chance, not genetic choice on the part of another human – raises the question whether we would ever be justified in intervening on a human embryo to correct a serious genetic disease. In my view, there is no ethical reason to refrain from undertaking necessary therapy intended for the benefit of that embryo, provided the potential benefits outweigh the risks and the parents provide informed consent. The question becomes much more difficult if what we are doing involves altering the human germ cell line, those genes that are passed on through ova and sperm from generation to generation. If a disease is caused by a defective gene and we correct that gene in the germ cell line of an embryo, all subsequent progeny of that embryo would be free of that disease. But some people think that we should never alter the human germ cell line. This would mean that in order to avoid an embryo inheriting a disease caused by a defective gene, we

would need to intervene on each embryo individually. While there is grave danger in allowing any intervention to alter the human germ cell line, the one situation in which this might be justified would be to cure a very serious, genetically inherited disease. We would need to take great care that our definition of such diseases was very narrowly construed, however, and did not open up a precedent for such interventions other than for this very limited purpose.

One danger of allowing alteration of the human germ cell line is that scientists will engage in genetic enhancement or disenhancement of embryos. Characteristics that might be subject to this interference include physical ones of height, eye and hair colour, or build. Lee Silver, in his book *Remaking Eden: How genetic engineering and cloning will transform the American family*, speaks of using the new genetic technologies to make two strains of humans – the 'gene rich' (genetically enhanced humans, especially with respect to intelligence) and the 'gene poor' (the genetically unenhanced – could we say natural?). He predicts that the gene rich will only want to reproduce with other gene rich persons and, consequently, the inequality will be perpetuated and extended. Many commentators believe that parents who are already willing to sacrifice a great deal in order to provide opportunities for their children – private schools, sports coaching or music lessons – would want to have their children's intelligence, sporting or musical ability genetically enhanced and would be willing to pay for this. They propose that in the long run it would probably be much less expensive than the methods used today. Should we prohibit such interventions? If we allow human cloning, would such interventions become more likely, or easier to carry out, or set a precedent that they are acceptable?

Perhaps the most surprising among the galaxy of astonishing feats that might be accomplished with the new genetic technologies is the possibility that we will be able to create a 'disease-proofed child'. In the same vein, Ben Bova, a science fiction writer, has recently speculated that the first person

to achieve immortality may already have been born, in that this person's genes will be able to be reprogrammed not to age or die. Should parents be allowed to have their children genetically modified in such ways?

The power to enhance intelligence can also be used to disenhance it. This possibility is most often discussed in the context of the need for a labour force for low-level, boring, repetitive jobs that those of natural or enhanced intelligence would not agree to perform. To undertake genetic disenhancement – to deliberately reduce intelligence or other characteristics of a person – would be a contemporary example of pure evil.

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There are reasons other than the risks involved for refraining from altering the human germ cell line. A requirement of profound respect for the human germ cell line also flows from at least three other facts: First, single genes can have multiple functions (the phenomenon called pleiotrophy) so we cannot know in advance the full possible impact of changing a single gene. Second, the human germ cell line is the common heritage of humankind handed to us by our ancestors and that we hold in trust for future generations. And, third, in the past major changes in the human germ cell line have occurred over vast time spans. We can now achieve comparable changes in nanoseconds; 'science time' is much faster than'ethics time'. At the least, we need to take 'ethics time' to decide what we must not do and may do. It is only now that it is possible to interfere with the essence of human life itself that we are faced with the question of what respect for our very nature requires that we must not do.

Although human reproductive cloning is not human reproduction, but human replication, it is often referred to as one of the new reproductive technologies. But is there a difference in kind between human reproductive cloning and the use of other new reproductive technologies or simply a difference in degree? We were at first horrified by the new reproductive technologies now widely used, but we relatively quickly came to a 'Let's

do it' stage. Will the same happen with human reproductive cloning? What is so striking is, as health law professor Laurie Andrews points out, that 'the time frame from horrified negation to "let's do it" is so much shorter'.

We cannot properly evaluate the impact of new reproductive technologies by looking at each in isolation. Rather, we must consider the effect of connecting them and the effect they will have on the social and cultural context in which they will be placed, and vice versa. We can gain insight about what the future might hold in this regard with respect to new reproductive technologies, including human reproductive cloning, when we are able to fully integrate them, by looking at the development of the Internet.

The technologies that now make up the Internet had each been around for half a century – fax machines since the 1930s, modems and radio phones since the 1940s – before the Internet became a (virtual) reality. An article in *The* [Montreal] *Gazette* describes it this way:

> The revolution came ... when we finally figured out how to connect them: how to make one fax machine connect with telephone lines and negotiate with another fax machine; how to let one modem talk to another on the telephone and agree between themselves how to work; how to take the big, crackling radio phones of old and connect them to networks that let you call someone who carries a phone tiny enough for his pocket. The trend for the future? Look around. 'The technologies are already here', [U.S. Nobel Prize laureate Arno] Penzias claims. 'They just haven't been connected yet.'

So it was only when the communication and information technologies were combined that they had a massive impact on our world, including its culture and values. The same is likely to be true for the new reproductive technologies. What would happen, for instance, were we to combine the technology for genetic enhancement of intelligence with that which makes possible a half-human half-chimpanzee, with – what, somewhat surprisingly, is the one missing link – the artificial uterus, which would make ectogenesis

(gestation of a child entirely outside a woman's uterus) possible? While most of us, it is to be hoped, could not imagine that we would ever accept human-animal hybrids as an ethical use of genetic technology, it is even more improbable that we would accept that women should carry them. It is, however, less improbable to imagine someone setting up an ectogenesis 'manufacturing plant' of such beings – unless, of course, we are prepared to say that some interventions that the new genetic technologies make possible are inherently wrong and must never be undertaken.

The least threatening use of human reproductive cloning is to use it to create a family. But, as Annas has pointed out, while many people 'love babies and technologies and most ... applaud the ability of the new assisted reproduction techniques to help infertile couples have children ... a bad way to protect the children who have been conceived and born with the assistance of the new reproductive techniques is simply to provide the adults involved with what they want.' We have shifted the emphasis in adoption practices from the rights of the biological parents to the welfare of the children and we must do the same in relation to the use of new reproductive technologies. Children must be moved to the centre of consideration in decision-making about the use of reproductive technologies, and nowhere more so than with respect to reproductive cloning. Some people who would allow human reproductive cloning believe, however, that it is wrong to argue that this type of cloning should be prohibited out of concern for the resulting child. Such an argument, they say, amounts to asserting the right of nothing to remain nothing.

Philosopher and ethicist Thomas Murray, in his sensitive and humane book *The Worth of a Child*, alerts us to the dangers that unbridled concepts of procreative liberty unmitigated by concerns for values can create: 'In the name of procreative liberty, an astonishing variety of arrangements for making and obtaining children have been defended. They are all in the service of making a family and so we should welcome them, say their defenders.' Such arrangements include what University

of Texas law professor John Robertson refers to as collaborative reproduction, which is often commercial collaborative reproduction – the sale of gametes and of embryos, and paid surrogate motherhood. As Murray points out, the champions of procreative liberty celebrate control and choice on the part of the parents, but with little concern for what this means with regard to harm to the children and to the values at the heart of family life:

> Good families are characterized more by acceptance than control. Furthermore, families are the pre-eminent realm of unchosen obligations. ... We may choose to have a child but – unless we are 'adopting' one of Robertson's cloned embryos – we do not choose to have this particular child with its interests, moods and manners.

It is not possible to explore here all the risks of human reproductive cloning to the cloned child or to important values that govern how we humans bond to each other in our first and predominant intimate relationship, that of the family. Some people who focus on risks to the cloned child as the main reason for prohibiting cloning argue that we would need so much human embryo experimentation, with the risks of injured or handicapped children being born as a result, that human cloning is not justified. And sometimes they add to this that the very large waste of human embryos that cloning would involve means it is not justified. This objection to cloning raises the issue of whether the major reason for prohibiting reproductive cloning is that it involves human embryo research. I propose that even if such research were not involved, human reproductive cloning is not ethically acceptable.

As well as physical risks to the child, there are also risks of psychological harm from a diminished sense of individuality and personal autonomy. Many teenagers have problems with individuation – separating themselves from their parents and seeing themselves as independent persons. Imagine the difficulty in this respect for a clone who has no genetic distance from the parent and, in all probability, looks physically like a carbon copy of his or her 'parent'. Imagine bringing up a child that was a clone of yourself and

correcting the mistakes you thought had been made by your parents or by you yourself. Consider the unrealistic expectations parents would place on the child. Then we can turn to the impact on the family of reproductive cloning. And consider the possibility that we would see a new form of genetic discrimination, between humans regarded as desirable enough to be cloned and the great unclonable masses, or possibly in the opposite direction, between the masses of the cloned and the genetically unique non-cloned people. One of the central problems of cloning, 'the devaluing of persons by depriving them of their uniqueness', has harmful consequences well beyond the devaluation itself.

The strongest case for human reproductive cloning is when it is done for compassionate reasons – for instance, to create matching organs or tissues to save the life of a dying child or to 'replace' that child. Annas, however, challenges our uncritical acceptance of this justification of cloning. He argues as follows:

Using the bodies of children to replicate them encourages all of us to devalue children and treat them as interchangeable commodities. ... The death of a child need no longer be a singular human tragedy, but, rather, an opportunity to replicate the no longer priceless or irreplaceable dead child. No one should have such dominion over a child, even a dead or dying child, as to use his or her genes to create the child's child.

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Parents who would clone their children are depriving these children of reproductive choice. They are treating their children as entities that can be split and replicated at their whim. Annas believes this is a stronger argument against cloning children than its biological novelty. It is hypocritical, he says, to argue that cloning expands the liberty and choices of would-be cloners, when it reduces the liberty and choices of the resulting child.

We can also look to the law that currently regulates intra-familial relationships, to see if it might provide insights on the ethics of human reproductive cloning. For instance, reproduction with blood relatives is prohibited by incest law, certainly for one reason and possibly for two. The certain reason is to avoid

dysgenesis, the genetic dangers for children born as a result of close relatives reproducing with each other. It is less certain that the prohibition of incest reflects a concern to maintain important family bonds and relationships that incest would threaten. Dysgenesis is not a problem in reproductive cloning, because it is genetic replication, not reproduction. Moreover, the crime of incest requires sexual intercourse, which is precisely what cloning excludes from reproduction. It is not as clear that the criminal law on incest reflects concern with protecting family bonds and relationships. But to the extent that it does, the use of this law – our most weighty, societal-values-establishing mechanism – to protect these relationships shows how important they are, not just to individuals but also to society. Damage to family bonds is a very relevant concern in relation to reproductive cloning.

In contrast to the law providing a message that human reproductive cloning should be prohibited, others argue that the courts, for instance, in the United States, have held that the state may not force a restrictive paradigm of the 'family' on people, and that constitutionally protected reproductive rights should include the right to found a family through cloning. A 'Note' in the *Harvard Law Review* articulates this view:

> Cloning should receive constitutional protection because it represents a conscious choice to bring a child into the world and to accept the social role of parenthood, thereby implicating the sort of deeply personal, family-related choices that trigger substantive due process protection. ... Despite its novelty, cloning would at least ensure a genetic bond between the parent and child, an important component of the social status of parenthood.

It remains to be seen whether the courts' views of what constitutes a family that will be given constitutional protection extends to rights to create one through cloning.

We have no idea how the radical reproductive and genetic departure that reproductive cloning represents would affect bonds and behaviour within the family, and its sense of itself, its past and its future. We often

differentiate bonds between intimates and bonds between strangers. A clone's relationship to his or her 'parent' and family is so far outside natural human experience, in a sense so intimate, that it is beyond even our human experience with bonds between strangers.

Although laboratory assistance in reproduction can be ethically justified in certain circumstances, I propose that its use should be regarded as an exception to the rule that natural reproduction is preferable. Those who wish to use a new technology such as reproductive cloning should have the burden of proving that to employ it is not inherently wrong, and, if it is not, that the benefits promised far outweigh the risks, and that the risks can be justified. (This approach requires, in particular, that we place the child at the centre of the decision-making.) Consequently, if we were to decide that human reproductive cloning is not inherently wrong, we must adopt a precautionary ethical principle, similar to that used in international environmental law. This would mean, as Annas explains, that the 'proponents of human cloning would have the burden of proving that there was some compelling contravailing need to benefit either current or future generations before such an experiment was permitted (for example, if the entire species were to become sterile)'. It merits noting that such a justification looks to the common good, not just the wishes of individuals. Our approach to human cloning – whether reproductive or therapeutic – must reflect societal values, not just the values of individuals or those of scientists and researchers. This raises the need for public consultation. And in order to engage ethically in that, we should recognize the difficulties inherent in undertaking it and ensure that it occurs in substance, not just appearance.

Suffice it to say that the issues and problems of human reproductive cloning with respect to the child and the family become even more complex and difficult, and raise additional matters of profound concern, when commercialization is involved – as would be inevitable were human reproductive cloning to be allowed.

Nature never contemplated needing safeguards against science such as human cloning. It was believed that there was a natural barrier to cloning an adult mammal, that genetic material in a somatic cell was irreversibly modified in such a way that you could not obtain a clone from it. Ian Wilmut, a research scientist, and his colleagues at the Rosslyn Institute in Glasgow showed, in creating Dolly, that this was not true. What does this new power require of us in fulfilling our human responsibility to hold nature 'in trust', in particular for future generations, but especially that part of nature that constitutes the fundamental nature of us? Perhaps the most profound question that has been asked is: If we were to undertake human cloning, what kind of creatures might we become?

Our anxiety about placing inhibitions on science may arise, in part, from the fact that we think the only way we can truly fulfil ourselves is through unlimited scientific progress. But the opposite might be true: We may need to refrain from certain actions such as human cloning in order to fully realize our humanness and humanity and to protect our human spirit.

If we proceed with human therapeutic cloning or human reproductive cloning, we will irreversibly change the moral or metaphysical reality and, therefore, our sense of the human spirit, which is crucial to our full human well-being. We need this reality to find meaning in human life and to surround human life, its essence and its transmission, with profound respect. Our human spirit is the only means we have to pass on this respect and meaning – our most important and oldest human values – to future generations. Cloning would pass on our physical life, but what would it do to the life of our human spirit?

We will not have the luxury of a trial run; any damage we cause to this moral or metaphysical reality is almost certain to be irreversible. We must, therefore, ask: Are we justified in causing the change in this reality that will inevitably result from undertaking human therapeutic cloning or human reproductive cloning? If not ever, at least, today or tomorrow?

References

Annas, G. J. 1998. The Shadowlands – secrets, lies and assisted reproduction. *New England Journal of Medicine*, Vol. 339, pp. 935–39.

_____. 1998. Why we should ban human cloning. *New England Journal of Medicine*, Vol. 339, pp. 122–25.

Blum, L. 1999. Going to the movies, eyes wide shut. *The National Post*, 30 July, p. B1.

Callahan, D. 1997. Cloning: The work not done. *Hastings Center Report*, Vol. 27, No. 5, p. 18.

Durkheim, E. 1951. *Suicide: A Study in Sociobiology*. J. A. Spaulding and G. Simpson (trans.). Glencoe, Ill., Free Press.

Gearhart, J. 1998. New potential for human embryonic stem cells. *Science*, Vol. 282, No. 5391, p. 1061.

Harvard Law Review. 1998. Human cloning and substantive due process (note). Vol. III, p. 2348.

Jonas, H. 1974. *Philosophical Essays: From Ancient Creed to Technological Man*. Englewood Cliffs, N.J., Prentice Hall.

Katz, K. D. 1997. The clonal child: Procreative liberty and asexual reproduction. *Albany Law Journal of Science and Technology*, Vol. 8, p. 1.

Kaye, H. L. 1998. Anxiety and genetic manipulation: A sociological view. *Perspectives in Biology and Medicine*, Vol. 41, No. 4, pp. 483–90.

Lewontin, R. C. 1997. The confusion over cloning. *New York Review of Books*, Vol. 44, p. 18.

McCabe, A. 1997. Landry Riles D'Aquino at World Economic Forum. *The Montreal Gazette*, 1 February, p. D5.

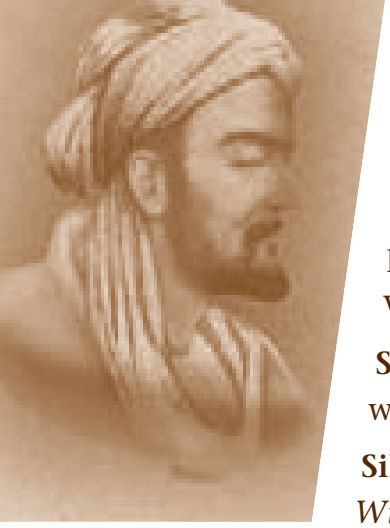
McGee, G. and Caplan, A. 1999. The ethics and politics of small sacrifices in stem cell research. *Kennedy Institute of Ethics Journal*, Vol. 9, No. 2, pp. 151–58.

Murray, T. H. 1996. *The Worth of a Child*. Berkeley, Calif., University of California Press.

National Bioethics Advisory Commission (U.S.). 1997. *Cloning Human Beings: Report and Recommendations of the National Bioethics Advisory Commission*, June. Rockville, Md., The Commission.

National Bioethics Advisory Commission (U.S.). 1999. *The Ethical Use of Human Stem Cells in Research*, September. Rockville, Md.: The Commission.

Nelkin, D. and Lindee, M. S. 1995. *The DNA Mystique: The Genes as a Cultural Icon*. New York, Freeman.



Ricœur, P. 1992. *Oneself as Another.* K. Blamey (trans.). Chicago, Ill., University of Chicago Press.

Robertson, J. A. 1986. Embryos, families and procreative liberty: The legal structure of the new reproduction. *Southern California Law Review,* Vol. 59, p. 939.

Shanner, L. 1995. The right to procreate: When rights claims have gone wrong. *McGill Law Journal,* Vol. 40, p. 823.

Silver, L. M. 1998. *Remaking Eden: How Genetic Engineering and Cloning Will Transform the American Family.* New York, Avon Books.

Wilmut, I. et al. 1997. Viable Offspring Derived from Fetal and Adult Mammalian Cells. *Nature,* Vol. 385, p. 810.

Chapter 4

Abdallah S. Daar and Peter A. Singer

*Pharmacogenetics and Geographical Ancestry: Implications for drug development and global health**

On 30 September 2004, Merck announced the worldwide withdrawal of Vioxx (rofecoxib), a multi-billion-dollar blockbuster analgesic drug, because of cardiovascular complications in those who took it for more than 18 months. It was the biggest ever withdrawal of a prescription medicine in the United States and wiped US$26.8 billion off Merck's market value that day. Was the worldwide withdrawal necessary? Or could Vioxx be resuscitated for selected populations?

Suppose that Merck had data to show that it was only individuals of north European ancestry who were affected by the adverse effects. Theoretically, Merck could still market Vioxx, with

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adequate warning labels to alert those people who were likely to be affected. Imagine that Vioxx was not just another analgesic but, for example, a powerful antiretroviral or another life-saving drug that was needed by, but unaffordable to, people in developing countries. Even if the drug was safe only for Indians and Han Chinese, that would constitute a market of over 2 billion people. Merck could license Indian and Chinese companies to manufacture such a drug for their own local markets. Merck's loss would be mitigated and pharmaceutical companies and patients in the developing world would benefit.

The completion of a good quality draft of the sequence of the euchromatic portion of the human genome was accompanied by a commentary in *Nature* in which the future of genomics was compared to a house (Collins et al., 2003). The question we ask here is: Who will live in that house? Is it only the 700 million or so people in the United States and Western Europe, or will the rest of the 6 billion people, who live mainly in the developing world, also be able to find room there?

In this article, we make two related arguments: first, that pharmacogenetics has significant relevance to the health of people in developing countries; and second, that for this benefit to be realized, we need to take into account not just differences between the genotypes of individuals, important as they are, but the differences in genotypes between different population groups.

We begin by identifying examples of how emerging knowledge about genetic and/or genomic variation is beginning to affect the pharmaceutical industry, and how pharmacogenetic strategies can be used to increase efficiency, cut costs, reduce adverse effects and increase the efficacy of drug-development pipelines. We document the trend towards using population-group genotypes in drug development and regulation, and discuss the implications of genetic differences that underlie variation in drug responses and disease susceptibility between population groups. We

highlight emerging genotyping studies that are being undertaken in various regions of the developing world and, if the vision materializes fully, the possible role of haplotype mapping in simplifying and reducing the cost of genotyping populations, potentially helping developing countries to benefit from knowledge of genetic diversity between populations. Finally, we explore how developing countries specifically will benefit from these new trends. We argue that pharmaceutical companies in developing countries will be able to harness pharmacogenetic principles and the knowledge of local genotype patterns to stimulate their industries, cut costs and generally improve the health of their populations.

Emerging industry trends

Pharmacogenetics itself is not a new discipline – it has been around for about 50 years (Kalow, 2002) (Box 1). What is new is that advances in genomics, particularly in methodology, have allowed us to merge pharmacogenetics with pharmacogenomics, improving our ability to identify the genetic causes of diseases and search for new drug targets. Today, several major pharmaceutical companies have teams that focus their research on the intersection between genetics, genomics and drug development, and some are already beginning to take genomic variation into account in their drug development pipelines. Although the idea of focusing clinical trials on subgroups of individuals is not new – stratification by disease subtype has always been a goal of medical research – the use of genetics in this context is new (Tate and Goldstein, 2004).

Box 1 | Drug response variation among individuals and populations

During the past 50 years of pharmacogenetic research (Meyer, 2004), we have learnt that variation between individuals that is influenced by genes and other factors is relevant to the efficacy of all drugs. We now know that metabolic enzymes are affected not only by SNPs (of which the human genome contains more than 10 million), but also by other genomic variation, such as gene duplications and deletions, mutations in regulatory genes, and probably by recently described large-scale copy number variations (Iafrate et al., 2004; Sebat et al., 2004). Increasing numbers of relevant polymorphisms are being discovered. Most relevant to our discussion, we also know that the frequencies and distributions of harmful and protective polymorphisms vary greatly between human populations (Goldstein et al., 2003; Schaeffeler et al., 2001; Wilson et al., 2001).

Given all of the above, it is valid to study traits that are predominantly expressed in specific populations (Nebert and Menon, 2001). Such studies might provide a molecular basis for population differences in drug-metabolizing enzymes (for example, cytochrome P450 (Xie et al., 2001; Meyer and Zanger, 1997), sulfotransferases (Weinshilboum and Otterness, 1994; Falany, 1997) and methyltransferases [Weinshilboum, 2003]), transporters (such as ABC1 [Schaeffeler et al., 2001; Ameyaw et al., 2001]), receptors (such as adrenergic receptors [Tate and Goldstein, 2004; Xie et al., 2001]) and other factors that are involved in differential drug responses and disease susceptibility. Many of the population-group differences that are documented are likely to have important medical and public-health implications (Taylor et al., 2004; Yancy et al., 2001; Exner et al., 2001).

Pharmacogenetics has so far had little impact on health-care in general, or on the pharmaceutical industry in particular. This is partly because pharmacogenetics has been thought of mainly as having boutique-style 'personal' applications that are unlikely to be relevant to the majority of people, particularly those in developing countries. We believe that this is about to change both with the adoption of pharmacogenetics *per se*, and because genetic differences between population groups – in addition to

differences between individuals – will be taken into account. The stimulus for the adoption of these complementary emerging trends in the developed world, and particularly in the United States, will come from regulatory changes, litigation, and patient demand based on accumulating scientific evidence of the validity of the pharmacogenetics approach (see the BiDil example below). In addition, there will always be market-based incentives if entrepreneurs identify an opportunity (Bloche, 2004).

The role of regulation in driving pharmacogenetics is best demonstrated by the recent actions of the United States Food and Drug Administration (FDA). The FDA has become a proactive advocate of pharmacogenetics and pharmacogenomics (Lesko and Woodcock, 2004). A few years ago it approved alosetron hydrochloride (Lotronex, GlaxoSmithKline) for irritable bowel syndrome, but the drug was quickly withdrawn voluntarily by GlaxoSmithKline because of adverse reactions. However, because of its efficacy, patients and physicians fought for Lotronex's return, and it was re-approved by the FDA in 2002 under restricted market terms. Now GlaxoSmithKline is studying the relationship between adverse events and genetic profiles as part of FDA-imposed post-marketing commitments (Webster et al., 2004).

In January 2003, the FDA called for greater scrutiny of data from subpopulations, asking drug testers to use the racial categories that have been specified by the Census Bureau, to ensure consistency when evaluating potential differences in responses to drugs (Food and Drug Administration, 2003). This is illustrated by a compelling example: a few years ago, the FDA rejected a fixed-dose combination of isosorbide dinitrate and hydralazine (now known as BiDil, NitroMed) because its efficacy in treating heart failure could not be demonstrated statistically in a clinical trial in the general population (Kahn, 2004). When it was tested exclusively in 1,050 self-identified African-American patients who had experienced heart failure (Franciosa et al., 2002), the results of this double-blind, randomized clinical trial were so impressive that in July 2004 the trial (which was endorsed by

the Association of Black Cardiologists) had to be stopped for ethical reasons; there was a significantly higher mortality rate in the placebo group than in the group given BiDil (Taylor et al., 2004). BiDil is now expected to be approved by the FDA in early 2005, as the first ever 'race-specific' therapy (Henig, 2004).

The role that litigation might play in driving the adoption of pharmacogenetics is illustrated by the Cassidy versus SmithKline Beecham case. This Pennsylvania class action suit alleged that SmithKline Beecham failed to warn doctors and the public that its vaccine against Lyme disease could trigger immune arthritis – an untreatable degenerative disease – in people who carry the HLA DR4+ marker, nearly a third of the United States population. Although both pre-marketing and post-marketing analyses by federal agencies have failed to confirm any increased risk from the vaccine, it was removed from the market in February 2002 as a result of plummeting sales that probably resulted from the controversy that surrounded the lawsuits (Marchant, 2003).

A number of pharmaceutical, biotechnology and genomics companies are now turning to pharmacogenetics in their 'personalized' medicine programmes, which are most relevant for the wealthy in the developed world. Some companies are prospectively collecting and analyzing samples from clinical trials to identify predictive SNPs. However, they are having difficulty in obtaining phenotypic data (for example, that relates to adverse effects) to link to information from DNA samples, and some companies are now working with the FDA to develop appropriate data-mining tools for clinical trial data. In the long term, it is perhaps more relevant to people in developing countries that pharmaceutical companies are on the lookout for genetic subgroups that could identify new targets for therapeutic drugs. Pfizer, for example, is particularly interested in hypertension-related genes in African Americans, and in diabetes-related genes that could account for the high rates of the disease in both Asian Indians and Native Americans. AstraZeneca is also looking for population differences in drug response in its clinical trials. If a drug were found to have

a 'profound effect' on a particular subpopulation, AstraZeneca would label and promote it accordingly; and 'if a population doesn't benefit, that could end up on the label too' (Holden, 2003).

Ancestry and phenotypic differences

Studies in population genetics have revealed a great deal of genetic variation within racial or ethnic subpopulations, but also substantial variation between the five main racial groups, which are based on continental ancestry. This variation has been demonstrated in three ways (Risch et al., 2002): first, ancestral tree diagrams carried out using population genetic data from indigenous groups consistently show that *Homo sapiens* has major branches that correspond to the five main groups. Second, clusters that have recently been inferred from multi-locus genetic data and other studies coincide closely with groups that are defined by self-identified race or continental ancestry (Mountain and Risch, 2004; Rosenberg et al., 2002). Third, low-frequency alleles are more likely to be race specific. Race-specific variants are particularly common among Africans, who have greater genetic variability than other racial groups but more low-frequency alleles (Risch et al., 2002). For observed phenotypic differences, self-identified race and continental ancestry often have relatively high predictive power compared to self-identified ethnicity. It is therefore likely that racial or ethnic categories will continue to be useful as long as such categorization 'explains' variation that is left unexplained by other factors (Mountain and Risch, 2004).

We must, however, be cautious as to how the results of such studies are interpreted and used (Foster and Sharp, 2004). We need a detailed understanding of each of the racial groups that are chosen for study, because the races that comprise the human species are far more heterogeneous than was previously thought. For example, individuals living in sub-Saharan rural Africa have close to 100% of what are called African alleles,

whereas African Americans living in the United States show about 26% Caucasian admixture (Lonjou and Morton, 1999). Some groups (for example, African-American, Caribbean and Panamanian populations) are likely to show a large degree of allelic diversity, whereas other groups (for example, sub-Saharan Africans, Inuits and Finns) are less genetically diverse. Old Amish individuals share more alleles than do individuals in other populations because they marry within their own community and as a result have a higher-than-average incidence of inborn errors of metabolism (Andreasen, 1983), as do some Arab consanguineous communities. Because of founder effects and enforced segregation, Ashkenazi Jews also share a large number of alleles.

A recent meta-analysis by Ioannidis et al. (2004) showed that genetic variants that are associated with disease predisposition might often have similar effects across racial groups. However, in an accompanying commentary, Goldstein and Hirschhorn (2004) point out that meta-analytic studies of this type are plagued by methodological concerns, and that the results presented by Ioannidis et al. do not mean that people from different parts of the world will, on average, have the same genetic predispositions to disease and will respond to medicines in the same way. It is well-known that allele frequencies of functional variants often differ substantially among groups that have different geographic ancestries. For example, of 38 polymorphisms that have been associated in at least two studies with a given drug response (Goldstein et al., 2003), two-thirds have significant allele-frequency differences between African Americans and Europeans, and many of the differences are substantial (see also Box 1).

Genotyping in developing countries

Although it is true that many developing countries are beset by poverty, a lack of clean water, diseases that are difficult to control, illiteracy and poor governance, it can be argued that they are the ones most in need of

emerging scientific and technological knowledge that might ameliorate their situations, by reducing costs and the adverse effects of drugs. At present, drugs that are tested on general populations in Europe and North America, and that are sometimes licensed on the basis of efficacy in only 30% of the subjects, are sold in developing countries without any idea of how effective or safe they are, and certainly without any regard for the local frequencies of genomic markers.

Therefore, it is not surprising that several developing countries are starting their own genotyping projects. For example, India and Thailand are both embarking on SNP-genotyping studies. Hosted by the Genome Institute of Singapore, an important regional initiative has recently brought scientists from China, India, Indonesia, Japan, Korea, Malaysia, Nepal, the Philippines, Singapore, Thailand and Taiwan to establish the Human Genome Organization (HUGO) Pacific Pan-Asian SNP Initiative, which is expected to begin in the middle of 2005. The goal of this initiative is to uncover the breadth of genetic diversity and the extent of genetic similarity within Asian populations. This information will form the basis for future studies in genomic medicine focused on Asian populations. Data from the Pan-Asian study will provide a platform for researchers in Asia to study why some populations seem predisposed to certain diseases, or do not respond to certain drugs. Cost reductions and new technologies are opening up the study to all researchers, including those with less well-developed research infrastructures.

Asia is not alone in such initiatives. Mexico has a newly-created, well-funded, federally mandated Institute of Genomic Medicine, headed by Gerardo Jimenez-Sanchez (2003). Genotyping the diverse Mexican populations is one of its top priorities.

Haplotype mapping

The relatively recent discovery of the haplotype structure of the human genome, and the effect that this has on SNP

inheritance, could help to simplify and reduce the cost of genotyping. When the International HapMap project is completed, it might be possible to use just 300,000–600,000 tag SNPs to define the most significant genetic variation. Genotyping just a handful of these carefully chosen SNPs in a chromosomal region may be enough to predict the remainder of the nearby common SNPs (The International HapMap Consortium, 2003).

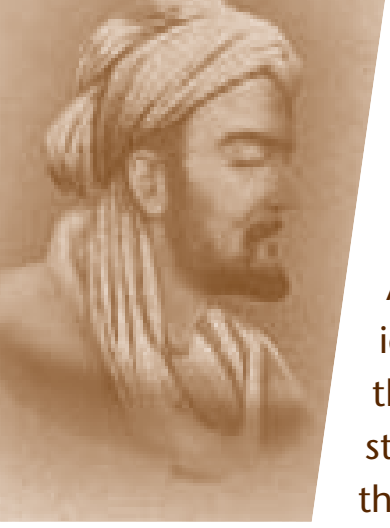
The HapMap itself does not define the genetic diversity of subgroups, but provides a useful framework to facilitate this. It will provide a resource, but not all of the answers. A cutting-edge example of the use of haplotype mapping to understand an association between complex disease and genetics is the work of the International Multiple Sclerosis Genetic Consortium (IMSGC). This example is relevant to our discussion of the value of genotyping for understanding diseases of subpopulations that have geographical ancestry in developing countries. Recognizing that multiple sclerosis (MS) is a complex genetic disorder, the IMSGC is setting out to define the most significant genetic variation that is associated with MS. By making use of the economic advantages that are provided by the emerging HapMap, as well as the falling costs of genotyping, the IMSGC expects to be able to cover the entire genome at high resolution (Sawcer et al., 2004). The consortium is also taking advantage of the observation that some groups are more prone to MS than others. It has long been known that African Americans have half the risk of developing classical MS compared with European Caucasians, and that sub-Saharan Africans rarely suffer from this condition. Providing that environmental influence is discounted, this indicates that it is the genetic contribution of Caucasians in African Americans that is responsible for the higher risk of MS in African Americans than in sub-Saharan Africans. By studying African Americans that have MS and identifying the genetic components that they have inherited from their European ancestors, the IMSGC hopes to identify regions of the genome that carry MS-susceptibility genes.

Through its value in drug development and its identification of populations that will respond favourably to a particular drug, pharmacogenetics will probably have an impact on global health, especially on neglected infectious diseases such as malaria, tuberculosis and HIV/AIDS (Pang, 2003). In the section below, we focus on specific ways in which drug development in, and for, developing countries will benefit from the recent trends discussed above.

Opportunities for developing countries

Only 16 of the 1,393 new drugs that were marketed between 1975 and 1999 were registered for diseases that predominantly affect people in developing countries, and three of those were for tuberculosis, which is not restricted to developing countries (Trouiller et al., 2002). In the future, pharmaceutical companies in the developed world will have to pay more attention to developing countries. There are at least two trends that will drive this change.

First, there is the need to gain deeper insight into the genetic basis for variable drug responses. As demand for drugs that are tailored to specific genotypes increases, pharmaceutical companies will increasingly depend on selling their products to segmented markets. Therefore, a deeper knowledge and cultivation of a wider and more extensive market outside North America and Europe will eventually be very important to them. If done correctly, this will in turn benefit people in developing countries. For pharmaceutical companies worldwide, developing countries are not only potentially huge markets for drug therapeutics but are also depositories of important human genetic diversity. Understanding this diversity is valuable because it better defines those population subgroups that will benefit more from a particular drug than others, and allows the detection of side-effects that might not be seen in populations that are mainly Caucasian. It can also help to ascertain disease predisposition.



It will therefore be increasingly important to include non-Caucasian populations in clinical trials. The interest by Pfizer and AstraZeneca in the genetics of African-American and Asian-Indian subgroups living in the United States to help to identify drug targets will probably not be adequate to satisfy the need for harnessing global genetic diversity. Genotyping studies of various populations from around the world will therefore become valuable.

Second, pharmaceutical companies in developing countries are themselves poised to make significant gains on the global market (Joshi, 2003). Big pharmaceutical companies can choose to view them as rivals to be thwarted or, alternatively, as companies with which to form mutually beneficial partnerships. For pharmaceutical companies in developing countries, pharmacogenetics might present an opportunity, especially if they learn to harness our increasing knowledge of the link between population genomic variation and health. It is true that internal economics limit the ability of many developing countries to capitalize on their genetic configurations. However, it could well be argued that, with annual *per capita* health-care expenditures as low as US$ 10–15, developing countries are the ones that have the greatest need for more cost-effective health-care strategies. This will enable these countries to not waste drugs on people who will not respond or who will be harmed, and to understand the genetic basis of disease predisposition, particularly of those diseases such as HIV/AIDS, which disproportionately affect people in developing countries and impose enormous burdens on their societies.

Although medical exploration in developing countries can expand the genetic diversity of subjects who take part in clinical trials that lead to drug development, pharmaceutical companies that attempt to harness this valuable genomic resource will not succeed unless they work closely with the authorities in developing countries, they act ethically, they are willing to share benefits, and they form partnerships with local researchers and pharmaceutical companies. Developing countries will not cooperate

if they feel that the benefits will go to others and that they are being used merely as instruments for that end. Clearly, the populations studied will also need to consent.

Drug resuscitation

In a recent review, Allen Roses described the potential useful applications of prospective efficacy and risk pharmacogenetics for drug development pipelines (Roses, 2004). He observed that new drugs that are withdrawn for safety reasons (and, by extension, for their lack of efficacy) in Phase IIA clinical trials by commercially driven pharmaceutical companies will probably not be used for other segments of the population because they would no longer be protected by patents. This might be the case for big pharmaceutical companies in the developed world, but it does represent an opportunity for pharmaceutical companies in developing countries to license these compounds and develop them, both for their local populations and for other people in the developing world who are either not genetically predisposed to the adverse effects or for whom efficacy can be demonstrated to a greater extent. This idea of 'resuscitation' of useful drugs for different populations is also, of course, applicable to post-marketing drug withdrawals, as we proposed above for Vioxx.

Indeed, it may now be time for incentives to be developed for just such drug resuscitations, perhaps in the form of public-private partnerships. Examples of drugs that have not been developed commercially in developed countries but that are useful in developing countries include ivermectin, which has been given as a gift by Merck to patients in the developing world who are suffering from onchocerciasis (see online link The Story of Mectizan). Another example is fosmidomycin, which is a natural antibiotic that was originally developed in the 1970s for bacterial infections but that was not commercially developed by its Japanese owners, the Fujisawa Pharmaceutical Company. In the late 1990s, a potential target for fosmidomycin was

identified in the partial genome sequence of the malaria parasite (Jomaa et al., 1999). Tests on mouse malaria confirmed the high level of efficacy of this drug, and fosmidomycin was rapidly tested in humans in Gabon. It has since been developed at very low cost, and is now part of the limited anti-malarial armamentarium that is at our disposal (Borrmann et al., 2004). A very relevant example that is based on pharmacogenetics and geographical ancestry is BiDil. BiDil could have been discarded because it did not have demonstrable efficacy when tested on a mixed population of United States patients. However, having been tested specifically on African Americans, it has been resuscitated for that population, and is obviously now of interest to Africans who share their geographical ancestry with African Americans.

The increasing numbers of public-private partnerships that are dedicated to finding treatments for major diseases of the poor, such as the Medicines for Malaria Venture, may contribute to this trend, as will the investment of US$ 275 million that the Bill and Melinda Gates Foundation has put into the Grand Challenges in Global Health programme (Varmus et al., 2003). The Institute for OneWorld Health, a US-based organization, aims to do something similar by identifying promising drug and vaccine candidates, developing them into safe, effective and affordable medicines, and then forming partnerships with companies and organizations in the developing world to manufacture and distribute them. The Drugs for Neglected Diseases Initiative is working along similar lines. Their models have not specifically taken into account genetic diversity, but with increasing knowledge, this might become a factor to consider in their surveys of drugs that are unlikely to be made commercial by big pharmaceutical companies.

Unexpected benefits

The compounds discovered in the research and development laboratories of developing countries may be of greater interest to big pharmaceutical

companies if they can be tested in selected minority subpopulations in developed countries. For example, compounds that are found to be effective in Asian Indians in India might be of interest to United States pharmaceutical companies to market to the significant population of Asian Indians in the United States. Conversely, drugs developed by smaller companies in the developed world for their minority populations could become useful for people in developing countries: NitroMed, which developed BiDil for African-American patients, might want to partner pharmaceutical companies in developing countries to test and market the drug in sub-Saharan Africa.

The increasing numbers of drugs that will need to be tested clinically on segmented populations will put further pressure on the already grossly over-burdened capacity to perform clinical trials, particularly in the United States. The large number of clinical trials being carried out in the United States at any one time is already increasing pressure to test these drugs in developing countries (Daar and Singer, 2002). This will drive the trend to partner with pharmaceutical companies and organizations that carry out contract research in developing countries. A beneficial outcome of such partnerships will be that the drugs being tested might be marketed locally in developing countries, in addition to the minority population of interest in the developed country. Furthermore, the results of clinical trials of drugs developed in the developed world and then tested on patients in developing countries will be more meaningful for those populations in developing countries in which they were tested. Conversely, the results of clinical trials carried out specifically in minority populations, such as the trial for BiDil tested on African Americans in the United States, will also be more meaningful for patients in those developing countries from which the minorities originated.

The cost efficiency associated with the drug development strategy of prospective efficacy pharmacogenetics (Roses, 2004) will result in less-expensive drugs for patients in

developing countries. When drugs are prescribed to groups who are unlikely to enjoy any benefit (and may also suffer adverse effects), the national cost of health-care is significantly higher than it need be otherwise. In Mexico, the doses of many drugs have to be altered significantly because they are either ineffective or too toxic at the levels recommended for the 'general' North American population. For example, L-asparaginase, an anti-cancer drug is given at lower doses in Mexico than in the United States to minimize toxicity (pancreatitis and/or hyperglycemia). By contrast, doses of the anti-cancer drug 6-mercaptopurine that are toxic in the United States population produce less-intense adverse effects in Mexican populations. So far, this is largely anecdotal, but the study of Mexican genomic diversity and its implications for public health is one of the priorities of the Mexican Institute of Genomic Medicine (Jimenez-Sanchez, 2003).

Pharmacogenetics may also feature in post-marketing surveillance. For example, some sub-Saharan African populations have a polymorphism in the ABCB1 (ATP-binding cassette, sub-family B (MDR/TAP), member 1) gene, which encodes the multidrug transporter P-glycoprotein, such that the carriers of this polymorphism might not benefit from antiretroviral therapy (Schaeffeler et al., 2001). This finding might translate into the closer scrutiny and the early withdrawal of those drugs that are found to be ineffective, saving many lives and millions of dollars. This will also stimulate the search for drugs that can bypass the effects of the polymorphism.

In terms of disease susceptibility, HIV demonstrates the importance of understanding genomic variation in human patients. A subpopulation of people with a 32-base pair deletion in the chemokine (C-C motif) receptor 5 (CCR5) gene (the CCR5-Δ32 mutant allele) are sero-negative and healthy, despite repeated exposure to HIV1 infection, because the mutation prevents expression of the CCR5 receptor on cell surfaces, which HIV uses to gain entry through mucosal surfaces. Strategies are being pursued to reduce

susceptibility to HIV infection by blocking the CCR5 receptor (Marmor, 2001). Recently, United States and Swiss researchers reported that coating the vaginal surfaces of macaque monkeys with an experimental drug that binds to CCR5 protects the monkeys against SIV (simian immunodeficiency virus) infection (Lederman et al., 2004).

Large-scale genotyping studies will give us greater insight into the distribution and frequency of genetic variation that has important public health implications.

Conclusion

Our increasing understanding of human genomic variation, and specifically its application in pharmacogenetics, might shift our focus away from interindividual differences towards interpopulation differences. In this article, we have made three main points. First, that pharmacogenetics can be made relevant to developing countries, where it might reduce national health-care bills. Essential drug lists in the future might have to take into account possible genomic variations between populations in developing countries. As often happens, for example with biotechnology (Thorsteinsdóttir et al., 2004), it is the people in developing countries (who make up about 85% of the world's population) who could benefit the most in the long term from cutting-edge science and technology (vaccines are a good example) (Acharya et al., 2003).

Our second point is that a deeper understanding of the genotypes of local populations with little admixture may make it possible, perhaps through the short-cuts and cost efficiencies promised by haplotype mapping, to predict drug responses without the need to test each individual. This application will require caution and validation, but it could make an important contribution to improving drug use in economically deprived populations before the advent of personalized medicine.

Finally, there are potential opportunities for pharmaceutical companies and contract-research organizations in developing countries to capitalize on emerging trends in genotyping and their application to understanding variable drug responses and disease susceptibility. Such opportunities, if applied properly, will benefit the health of people in developing countries.

Future outlook

We have some way to go before the vision of real benefits of pharmacogenetics to developing countries materializes. Substantial knowledge gaps will need to be addressed by well-designed studies in multiple populations (Collins, 2004). There are also conceptual and technical problems that need to be resolved, and the use of population groups – at least as currently conceived in terms of race and other unsatisfactory descriptors that conflate with social constructions – is fraught with ethical and social problems that will need to be addressed with interdisciplinary research. The most satisfactory term for population groups at present is emerging as 'geographical ancestry'; but as data accumulate, we may discover other terms for communities of common ancestry that are more scientifically accurate and that avoid social constructions completely, making it possible to move forward with less likelihood of controversy. We need to change the paradigm from 'race' to human genome variation (Royal and Dunston, 2004).

If we are to help reduce global health inequities we must continue to support efforts to define the nature of human variation across the world, focused primarily on medical goals (Collins, 2004). We need to formulate clear, scientifically accurate messages to educate researchers, health-care professionals and the general public on the connections between race, ethnicity, genetics and health. For developing countries not to be left behind, to harness useful knowledge for their populations, and to avoid pitfalls, their researchers and policy-makers must participate in this important

discourse as early as possible. We need an innovative global approach, such as the proposed Global Genomics Initiative (Acharya et al., 2004), to bring together industry, academia, non-governmental organizations and international organizations, such as the World Health Organization, to examine how pharmacogenetics and pharmacogenomics can best be harnessed to improve the health of people in developing countries. Pharmaceutical and biotechnology companies from both developed and developing countries should plan for the long term and consider the realities of the developing world, because that is where there will be the largest population growth, disease burden, drug demand and future markets. If markets won't work, public-private partnerships will probably be created to address the important needs of developing countries. Academics should begin empirical case studies of genotyping projects in developing countries and of early applications of pharmacogenetics in both developed and developing countries to identify good practices and avoid pitfalls.

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References

Acharya, T., Daar, A. S. and Singer, P. A. 2003. Biotechnology and the UN's millennium development goals. *Nature Biotechnology*, Vol. 21, pp. 1434–1436.

Acharya, T., Daar, A. S., Thorsteinsdóttir, T., Dowdeswell, E. and Singer, P. A. 2004. Strengthening the role of genomics in global health. *PLoS Med.* Vol. 1, e40.

Ameyaw, M. M. et al. 2001. MDR1 Pharmacogenetics: Frequency of the C3435T mutation in exon 26 is significantly influenced by ethnicity. *Pharmacogenetics*, Vol. 11, pp. 217–221.

Andreasen, N. C. 1983. The Amish: A naturalistic laboratory for epidemiological and genetic research. *Am. J. Psychiatry*, Vol. 140, pp. 75–76.

Bloche, M. G. 2004. Race-based therapeutics. *N. Eng. J. Med.*, Vol. 351, pp. 2035–2037.

Borrmann, S. et al. 2004. Fosmidomycin-clindamycin for the treatment of plasmodium falciparum malaria. *J. Infect.* Dis., Vol. 190, pp. 1534–1540.

Carson, P., Ziesche, S., Johnson, G. and Cohn, J. N. 1999. Racial differences in response to therapy for heart failure: Analysis of the vasodilator-heart failure trials. Vasodilator-Heart Failure Trial Study Group. *J. Card. Fail.*, Vol. 5, pp. 178–187.

Collins, F. S., Green, E. D., Guttmacher, A. E. and Guyer, M. S. 2003. A vision for the future of genomics research. *Nature*, Vol. 422, pp. 35–47.

Collins, F. S. 2004. What we do and don't know about 'race', 'ethnicity', genetics and health at the dawn of the genome era. *Nature Genet.*, Vol. 36, S13–S15.

Daar, A. S. and Singer, P. A. 2002. Human capital is key to research ethics. *Science and Development Network*. http://www.scidev.net (Accessed 30 January 2006).

Exner, D. V., Dries, D. L., Domanski, M. J. and Cohn, J. N. 2001. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. *N. Engl. J. Med.*, Vol. 344, pp. 1351–1357.

Falany, C. N. 1997. Enzymology of human cytosolic sulfotransferases. *FASEB J.* Vol. 11, pp. 206–216.

Food and Drug Administration. 2003. Draft guidance for industry on the collection of race and ethnicity data in clinical trials for FDA regulated products. *Fed. Regist.*, Vol. 68, pp. 4788–4789.

Foster, M. W. and Sharp, R. R. 2004. Beyond race: Towards a whole-genome perspective on human populations and genetic variation. *Nature Rev. Genet.*, Vol. 5, pp. 790–796.

Franciosa, J. A. et al. 2002. African-American Heart Failure Trial (A HeFT): Rationale, design and methodology. *J. Card. Fail.*, Vol. 8, pp. 128–135.

Goldstein, D. B., Tate, S. K. and Sisodiya, S. M. 2003. Pharmacogenetics goes genomic. *Nature Rev. Genet.*, Vol. 4, pp. 937–947.

Goldstein, D. B. and Hirschhorn, J. N. 2004. In genetic control of disease, does 'race' matter? *Nature Genet.*, Vol. 36, pp. 1243–1244.

Henig, R. M. 10 October 2004. The genome in black and white (and gray). *New York Times* (*New York*), p. 47.

Holden, C. 2003. Race and medicine. *Science*, Vol. 302, pp. 594–596.

Iafrate, A. J. et al. 2004. Detection of large-scale variation in the human genome. *Nature Genet.*, Vol. 36, pp. 949–951.

The International HapMap Consortium. 2003. The International HapMap Project. *Nature*, Vol. 426, pp. 789–796.

Ioannidis, J. P. A., Ntzani, E. E. and Trikalino, T. A. 2004. 'Racial' differences in genetic effects for complex diseases. *Nature Genet.*, Vol. 36, pp. 1312–1318.

Jimenez-Sanchez, G. 2003. Developing a platform for genomic medicine in Mexico. *Science*, Vol. 300, pp. 295–296.

Jomaa, H. et al. 1999. Inhibitors of the nonmevalonate pathway of isoprenoid biosynthesis as antimalarial drugs. *Science*, Vol. 285, pp. 1573–1576.

Joshi, H. N. 1 January 2003. Analysis of the Indian pharmaceutical industry with emphasis on opportunities in 2005. *Pharmaceutical Technology (New Jersey)*, pp. 74–94.

Kahn, J. 2004. How a drug becomes 'ethnic': Law, commerce, and the production of racial categories in medicine. *Yale J. Health Policy Law Ethics.*, Vol. 4, pp. 1–46.

Kalow, W. 2002. Pharmacogenetics and personalised medicine. *Fundam. Clin. Pharmacol.*, Vol. 16, pp. 337–342.

Lederman, M. M. et al. 2004. Prevention of vaginal SHIV transmission in rhesus macaques through inhibition of CCR5. *Science*, Vol. 306, pp. 485–487.

Lesko, L. J. and Woodcock, J. 2004. Translation of pharmacogenomics and pharmacogenetics: A regulatory perspective. *Nature Rev. Drug Discov.*, Vol. 3, pp. 763–769.

Lonjou, C., Collins, A. and Morton, N. E. 1999. Allelic associations between marker loci. *Proc. Natl Acad. Sci. USA*, Vol. 96, pp. 1621–1626.

Marchant, G. E. 2003. Genomics and toxic substances: Part II – genetic susceptibility to environmental agents. *Environ. Law Rep.*, Vol. 33, pp. 10641–10776.

Marmor, M. et al. 2001. Homozygous and heterozygous CCR5-Δ32 genotypes are associated with resistance to HIV infection. *J. Acquir. Immune Defic. Syndr.*, Vol. 27, pp. 472–481.

Meyer, U. A. and Zanger, U. M. 1997. Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu. Rev. Pharmacol. Toxicol.*, Vol. 37, pp. 269–296.

Meyer, U. A. Pharmacogenetics – five decades of therapeutic lessons from genetic diversity. 2004. *Proc. Natl Acad. Sci. USA*, Vol. 101, pp. 9127–9132.

Mountain, J. L. and Risch, N. 2004. Assessing genetic contributions to phenotypic differences among 'racial' and 'ethnic' groups. *Nature Genet.*, Vol. 36, S48–S53.

Nebert, D. W. and Menon, A. G. 2001. Pharmacogenomics, ethnicity, and susceptibility genes. *Pharmacogenomics Journal*, Vol. 1, pp. 19–22.

Pang, T. 2003. Impact of pharmacogenomics on neglected diseases of the developing world. *Am. J. Pharmacogenomics.*, Vol. 3, pp. 393–398.

Risch, N., Burchard, E., Ziv E. and Tang H. 2002. Categorization of humans in biomedical research: genes, race and disease. *Genome Biol.*, Vol. 3, comment 2007.1–comment 2007.12.

Rosenberg, N. A. et al. 2002 Genetic structure of human populations. *Science*, Vol. 298, pp. 2381–2385.

Roses, A. D. 2004. Pharmacogenetics and drug development: The path to safer and more effective drugs. *Nature Rev. Genet.*, Vol. 5, pp. 645–656.

Royal, C. D. M. and Dunston, G. M. 2004. Changing the paradigm from 'race' to human genome variation. *Nature Genet.*, Vol. 36, S5–S7.

Sawcer, S. J. et al. 2004. Enhancing linkage analysis of complex disorders: an evaluation of high-density genotyping. *Hum. Mol. Genet.*, Vol. 13, pp. 1943–1949.

Schaeffeler, E. et al. 2001. Frequency of C3435T polymorphism of MDRI gene in African people. *Lancet*, Vol. 358, pp. 383–384.

Sebat, J. et al. 2004. Large-scale copy number polymorphism in the human genome. *Science*, Vol. 305, pp. 525–528.

Tate, S. K. and Goldstein, D. B. 2004. Will tomorrow's medicines work for everyone? *Nature Genet.*, Vol. 36, S34–S42.

Taylor, A. L. et al. 2004. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N. Eng. J. Med.*, Vol. 351, pp. 2049–2057.

Thorsteinsdóttir, H., Quach, U., Daar, A. S. and Singer, P. A. 2004. Conclusions: Promoting biotechnology innovation in developing countries. *Nature Biotechnology*, Vol. 22, DC48–DC52.

Trouiller, P. et al. 2002. Drug development for neglected diseases: a deficient market and a public-health policy failure. *Lancet*, Vol. 359, pp. 2188–2194.

Varmus, H. et al. 2003. Grand challenges in global health. *Science*, Vol. 302, pp. 398–399.

Webster, W., Martin, P., Lewis, G. and Smart, A. 2004. Integrating pharmacogenetics into society: in search of a model. *Nature Rev. Genet.*, Vol. 5, pp. 663–669.

Weinshilboum, R. M. and Otterness, D. M. 1994. Sulphotransferase enzymes. *Handbook of Experimental Pharmacology*, Vol. 112. Kauffman, F. C. (ed.), Berlin, Springer, pp. 45–78.

Weinshilboum, R. 2003. Inheritance and drug response. *N. Eng. J. Med.*, Vol. 348, pp. 529–537.

Wilson, J. F. et al. 2001. Population genetic structure of variable drug response. *Nature Genet.*, Vol. 29, pp. 265–269.

Xie, H. G., Kim, R. B., Wood, A. J. and Stein, C. M. 2001. Molecular basis of ethnic differences in drug disposition and response. *Annu. Rev. Pharmacol. Toxicol.*, Vol. 41, pp. 815–850.

Yancy, C. W. et al. 2001. Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. *N. Engl. J. Med.*, Vol. 344, pp. 1358–1365.

Chapter 5

Abdallah S. Daar and Louisa E. Chapman

*Xenotransplantation**

Xenotransplantation is the transplantation of living cells, tissues or organs between members of different species. In the human clinical context, xenotransplantation refers to the use of living biological material from any nonhuman species in human recipients for therapeutic purposes. The practice began with attempts to develop whole animal organs as 'spare parts' to replace failing human organs. Current efforts also involve cellular applications.

Xenotransplantation is currently experimental. However, some applications have progressed to clinical trials in humans and could become available therapeutic options in the early twenty-first century. Decisions about such trials must draw on areas in which science currently offers inexact guidance, raising interrelated issues of ethics and social policy. Forging consensus on appropriate public policy is multinational in scope, often pits different stakeholders against each other, and has triggered heated debate among scientists, ethicists and the public. In this respect, the issues raised by the exercise of social policy-making for xenotransplantation provide a good case study for more

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general discussions of how biomedical technology should be developed and implemented.

Organ transplantation has been hailed as one of the most remarkable achievements in medical history. The original kidney transplant successes of the mid-1950s were between genetically identical human twins whose immune systems would not recognize each other's organs as genetically foreign (and therefore would not reject them). Soon thereafter, kidneys for transplantation were obtained from non-twin siblings, from unrelated living donors and, finally, from cadavers. These transplants between members of the same species are known as *allotransplants* and, apart from the rare identical twin transplants, all require some form of manipulation of the recipients' immune systems to prevent rejection of the donated organ.

Medical advances, particularly the discovery of powerful new immunosuppressive drugs, have greatly increased the number of transplants performed worldwide. Today, where facilities and expertise are available, it is fairly routine to transplant kidneys, hearts, livers, lungs, and other organs and tissues between human beings. However, this very success has created a disparity between the demand and supply of organs. As a result, thousands of patients die every year while waiting to receive a suitable organ for transplant. The situation is particularly severe in developing countries. Were xenotransplantation to become an effective and inexpensive method of addressing end-stage organ failure, however, the same social and economic issues that limit the ability to maintain transplant programmes in developing countries today will hinder efforts to develop and maintain xenotransplantation programmes. Basic health care needs (such as vaccination, basic diagnostics, and drugs) and the need for access to clean water will compete with any advanced technology for limited health-care dollars.

Allotransplantation raised important ethical issues, many of which continue to be debated (Dossetor and Daar, 2001). While xenotransplantation

raises similar issues, especially in terms of equity of access and diversion of resources, it also raises issues pertaining to human rights, animal welfare and public health risks.

Xenotransplantation defined

While consensus is not universal, xenotransplantation is defined as 'any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman animal source; or (b) human body fluids, cells, tissues, or organs that have had *ex vivo* contact with live nonhuman animal cells, tissues, or organs.' This is the definition adopted by the U.S. Public Health Services, and the Council of Europe has a similar one. This definition would include transplantation of an animal heart into a patient with heart failure, implantation of pancreatic islets for people with diabetes, circulation of blood from a patient with acute liver failure through a nonhuman liver or a device containing nonhuman liver cells, or the treatment of burn patients using human skin cells that have been grown *ex vivo* (outside the body) over a layer of mouse feeder cells. The transplantation of inert animal tissue (such as pig heart valves) does not fall under this definition.

Scientific and clinical state-of-the-art: Continuing challenges

Tables 1 and 2 summarize the attempts at clinical xeno-transplantation since the 1960s. With the exception of the inexplicable survival for nine months of a kidney transplanted from a chimpanzee into a human recipient in the 1960s, all whole-organ xenotransplants have failed rapidly, despite massive immunosuppression of the human recipients. In contrast, a number of preclinical trials of cellular therapies have shown enough promise to justify progressing to clinical

trials. These include neural-cell transplants to treat disorders such as Parkinson's disease, intractable epilepsy and other degenerative neurologic diseases (Fink et al., 2000). There have also been attempts at perfusing the blood of patients in acute liver failure *ex vivo* through nonhuman animal livers until a human liver becomes available or the patient recovers (Chari et al., 1994). However, as of April 2003, no xenotransplantation application has demonstrated a high enough level of efficacy in clinical trials to allow progression to general clinical adoption.

Table 1: ***Summary of clinical organ xenotransplantation during the 1960s, 1970s and 1980s***

	Year	Source Animal	Number	Investigator
Kidney	1964	Chimpanzee	12	Reemtsma
	1964	Monkey	1	Reemtsma
	1964	Baboon	1	Hitchcock
	1964	Baboon	6	Starzl
	1964	Chimpanzee	1	Hume
	1964	Chimpanzee	3	Traeger
	1965	Chimpanzee	2	Goldsmith
	1966	Chimpanzee	1	Cortesini
Heart	1964	Chimpanzee	1	Hardy
	1968	Sheep	1	Cooley
	1968	Pig	1	Ross
	1968	Pig	1	Ross
	1969	Chimpanzee	1	Marion
	1977	Baboon	1	Barnard
	1977	Chimpanzee	1	Barnard
	1984	Baboon	1	Bailey
Liver	1966	Chimpanzee	1	Starzl
	1969	Chimpanzee	2	Starzl
	1969	Baboon	1	Bertoye
	1970	Baboon	1	Leger
	1970	Baboon	1	Marion
	1971	Baboon	1	Poyet
	1971	Baboon	1	Motin
	1974	Chimpanzee	1	Starzl

Source: Council of Europe Working Party on Xenotransplantation. Report on the state of the art in the field of xenotransplantation. February 21, 2003

Table 2: ***Summary of clinical trials on organ and cell xenotransplantation during the 1990's.***

	Graft	Indication	Number	Country	Presently including patients
Organ transplantation	Pig heart	Heart failure, bridging procedure	1	Poland	No
	Baboon liver	Hepatitis B with liver failure	2	USA	No
	Pig liver	Liver failure, bridging procedure	1	USA	No
Cellular grafts	Neonatal bovine cromaffine cells	Pain	more than 100	Poland, Czech Republic, Switzerland & USA	No?
	Encapsulated transgenic hamster cells	ALS	6	Switzerland	No?
	Fetal porcine neurons	Parkinson Huntington Epilepsy Stroke	21 12 3 3	USA USA USA USA	Yes Yes Yes Yes
	Fetal porcine islets	Diabetes	10	Sweden	No
	Neonatal porcine islets	Diabetes	6	New Zealand	No
	Fetal rabbit islets	Diabetes	Several 100	Russia	Yes
	Baboon bone marrow	HIV	1	USA	No

Source: Council of Europe Working Party on Xenotransplantation. Report on the state of the art in the field of xenotransplantation. February 21, 2003

Hyperacute rejection. The initial technical obstacle to xenotransplantation is the phenomenon of hyperacute rejection, which occurs when tissue is transplanted between two distant (discordant) species, for example between pigs and humans. *Hyperacute rejection* is swifter and more severe than the acute rejection response usually seen in transplants

between individuals of the same species. Xenotransplant rejection responses are, however, also less severe in transplants between members of closely related (concordant) species, such as between rats and mice. A carbohydrate molecule known as Gal alpha-1, 3 Gal (alpha-gal) is present on all cells of most mammalian species, including pigs, which at present are considered the most likely source-animal species. Humans and closely related old-world primates such as chimpanzees lack alpha-gal, but have naturally occurring antibodies that recognize it as foreign. In hyperacute rejection these antibodies would react against the alpha-gal on pig cells, causing the blood to clot (thrombosis) and the transplanted organ to die within minutes.

Activation of complement, a substance found in blood, is part of the normal defence mechanism against foreign tissue or microbes. The presence of chemical substances that inactivate complement when its work is done normally prevents thrombosis. These complement factor regulatory proteins (CRPs) are species-specific. Thus one of the scientific responses to the challenge of hyperacute rejection has been to create transgenic pigs in which the genes for various human CRPs have been incorporated into the pig's genome, and thus prevent thrombosis. Experiments in which tissue from these transgenic pigs was transplanted into nonhuman primates have shown better graft survival rates than those using tissue from unmodified pigs, raising hopes that similar improved results would be reproduced in human recipients.

Another genetic approach to dealing with hyperacute rejection has aimed to alter the expression of the alpha-gal molecule on pig tissue by inserting genes that result in carbohydrate remodeling (Sandrin et al.,1995); by reducing the expression of alpha-gal (Sharma et al., 1996); or by 'knocking out' (removing) the gene for the enzyme that is involved in making alpha-gal (Tearle et al., 1996). A double knock-out pig (a pig in which both copies of the gene have been deleted from its genome) was announced in 2002 (Phelps et al., 2003). Others have focused on reducing the massive inflammatory responses.

Other immunological challenges. Hyperacute rejection is only one challenge facing xenotransplantation. Even if hyperacute rejection can be avoided, progressive phases of rejection would follow, including acute vascular rejection, cellular rejection, and chronic rejection.

Related research focuses on attempts to manipulate the immune system of higher animals in ways that would make it 'tolerate' one, or a few, foreign antigens without paralyzing the whole immune system. Should immunological tolerance be achieved in humans, it would become possible to transplant organs without administering the large doses of powerful immunosuppressive drugs that leave the recipients vulnerable to dangerous infections.

Physiological barriers. Physiological barriers may also stand in the way of successful xenotransplantation. For example, there is serious doubt that a pig liver will be able to sustain a human being for long. The liver is not only a detoxifying and storage organ, it is the main factory in the body for the manufacture of a large number of crucial molecules, including proteins such as albumin and clotting factors. Many of these are species-specific and will function inadequately in humans (Hammer and Thein, 2001), and some may also evoke immune reactions. In contrast, porcine insulin has successfully treated human diabetics; thus porcine pancreatic islet transplantation may offer human diabetics hope for a cure.

Xenogeneic infections

Another reason for caution is that infections not normally encountered in humans might be transmitted from source animals to human recipients. In addition to the risk to the recipient, there is a theoretical risk that an infected recipient could transmit the infection to others. Of particular concern in this regard are infectious agents such as retroviruses that result in persistent infections and remain clinically quiescent for

long periods before causing identifiable disease. During that 'silent' period they can be transmitted from person to person, infecting many people before the danger is recognized.

In the past, animal viruses, such as Nipah virus and avian influenza, have been known to infect humans, resulting in outbreaks of disease of limited scope and duration (CDC, 1998, 1999). Of even greater concern is evidence that viruses once restricted to a nonhuman host species may infect and adapt to humans as a host species, as is theorized to have occurred with the HIV/AIDS pandemic (Hahn et al., 2000). There is some controversy about whether nonhuman primates are more likely than other species to transmit dangerous infections to humans (Chapman et al, 1995). In response to widespread concern, the U.S. Food and Drug Administration produced an advisory in April 1999 against the use of primates as source animals pending adequate demonstration of safety.

Exogenous infection (infections from agents passed among animals by contagion) can theoretically be controlled by eliminating them from the source animals. More uncertainty exists about the significance of endogenous retroviruses, which exist as part of the genetic material of humans, nonhuman primates, pigs, mice, and perhaps all animals. Endogenous retroviruses are passed from one animal to another through inheritance. Unable to cause active infection in the host animal, many can produce a virus capable of causing infection in cells from other species in the laboratory. Thus, living biological material devoid of recognized microbes has an innate infectious potential of uncertain significance for xenotransplantation. Specifically, both pigs and nonhuman primates have been shown to have endogenous retroviruses that can infect human cells in the laboratory.

Since the pig is the most likely source animal for human clinical xenotransplants, endogenous retroviruses of pigs have become a major focus of research. Porcine endogenous retroviruses (PERV) exist in the genomes of all pigs.

Several variants of PERV have been characterized that vary in their infectivity. It would be difficult, but perhaps possible, to eliminate PERV through breeding or genetic manipulations (Patience et al., 1997; Stoye, 1998).

In animal experiments, short-lived (but nonclinically obvious) replicative infections have been documented (van der Laan et al., 2000), and PERV can be transmitted from pig cells to human cells when they are cultured together in the laboratory (Patience et al., 1998; Wilson et al., 1998), but there is currently no convincing evidence that PERV can cause infections leading to disease in humans. This does not, of course, exclude the possibility that it may be capable of doing so given the right circumstances.

Human patients previously exposed to pig tissue. In the past decade or so a small but significant number of patients have been exposed to various experimental forms of xenotransplantation. Several studies of these patients have found no evidence of PERV infection, despite evidence that many of those exposed exhibited 'microchimerism' (they had small numbers of pig cells in their bodies which provided ongoing exposure to PERV). While many scientists do not consider that these studies conclusively establish the absence of infectious disease risk associated with xenotransplantation, they are reassuring to some extent.

Ethical, social and economic issues

Research and development costs for any major new technology, including xenotransplantation, can be high. If xenotransplantation progresses from experimentation into clinical practice, the final cost is uncertain. Even beyond the development costs, many factors will contribute to the expense of a clinical xenotransplantation programme, including rearing specific infection-free source animals, laboratory tests for early diagnosis of infection, specialized staff, and maintaining monitoring and surveillance

regimes. Costs will also be determined by companies owning intellectual property rights to the technologies employed, the size of the market, and so on. Whether this cost will exceed the current costs of medication and extended hospital care for patients awaiting allotransplants is uncertain. It seems likely, however, that xenotransplantation, like allotransplantation, would initially benefit only a privileged few.

It has been argued that xenotransplantation efforts could be justified only if large numbers of patients could benefit at reasonable cost and with no significant diversion of resources from the health-care system. In this light, efforts to develop applications of porcine pancreatic islets for functional cure of type I diabetes mellitus are the most easily justified. While many applications of xenotransplantation research would benefit relatively few patients, diabetes mellitus affects a large number of people and poses substantial costs to society, both in terms of economics and in years of productive life lost.

Precautionary principle versus risk-benefit analysis. It is possible that the public may eventually benefit indirectly from successful widespread xenotransplantation due to a decrease in the societal burdens of health-care costs and years of productive lives lost due to chronic diseases. The public may, however, also be put at risk of infections. As a result, although the extent of the risk is not clear, many nations have regulations that would allow xenotransplant clinical trials only when using husbandry methods that eliminate exogenous infectious agents from source animals prior to transplantation, and that would ensure ongoing monitoring of recipients.

As long as uncertainty about the risk to society exists, different constituencies will perceive the same scientific data on public risk in different ways. Those basing their public-policy decisions on traditional risk-benefit analysis would tend to favour patients, perhaps at the expense of the public. Many clinicians and scientists in the transplant community do

this instinctively, emphasizing the benefits in terms of a moral imperative to ameliorate suffering and save lives. This attitude is reflected by the Institute of Medicine's statement that 'our own humanity is diminished if, in order to protect ourselves, we turn away from others whose suffering is both clearly visible ... and ... devastating in ... impact ... we are morally obliged, not only as individuals but as a community, to accept some risk to ourselves to save our fellow human beings from more certain harm' (Institute of Medicine, 1996, p. 71). On the other hand, those who would base decisions on the 'precautionary principle' (of which there are several versions) would tend to pay more attention to the public interest, perhaps at the expense of needy patients (Daar, 2001).

The precautionary principle originated in environmental risk discourse but has been adopted into health-policy discussions partly because of the history of infections with agents that cause AIDS, mad cow disease and so on. It is easy to misunderstand, misquote and misuse this concept as there is no single definition. There are two well known formulations. The first, from Article 15 of the United Nation's 1992 Rio Declaration on Environment and Development, states: 'In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.' The second, the so-called Wingspread Declaration, states: 'When an activity raises threats of harm to human health or the environment, precautionary measures should be taken, even if some cause-and-effect relationships are not established scientifically.'

As can be expected, the precautionary principle has become a subject of intense scholarly debate and ethical analysis (Saner, 2002). Some have argued that to be true to itself the precautionary approach requires risk-risk analysis, which would suggest an alternative formulation for the principle along the

lines, 'Public health and environmental policies should attempt to minimize net risks to public health and the environment based on the best available scientific information and their net anticipated cost to society.' (Goklany, 2002, p. 1075)

Animal issues. The great British reformer Jeremy Bentham, a key figure in the development of utilitarian ethics, was also one of the earliest advocates for the humane treatment of animals. In 1780 he asked two fundamental questions: (1) 'The question is not "Can they reason?" nor "Can they talk?" but "Can they suffer?"' and (2) 'What insuperable line prevents us from extending moral regard to animals?'

Since Bentham's time, it has become widely recognized that all vertebrates essentially perceive pain in the same way. Some argue that animals can also suffer. Animals reared in stressful conditions in captivity experience fear, boredom, isolation and separation anxiety. Recent evidence indicates that the great apes are capable of using language, including human words (BBC), and also exhibit forms of culture. The emotional repertoire of nonhuman primates, according to ethologists Jane Goodall and Dian Fossey, includes love, sorrow and jealousy. These attributes have led some to argue that such animals are more than just sentient beings and that they possess intrinsic value. If so, then they must have rights. To some, ignoring these rights is a form of speciesism, a term analogous to racism, and a growing minority are embracing this view.

The awareness of such qualities of animal life raises serious questions: What is it in humans that bestows on us the right to kill an animal for our own self-interest? Is it our complex use of language and tools? Is it our rationality, intentionality, consciousness, conscience or empathy? Immanuel Kant argued that all nonhuman animals can be regarded as means to ends, and that only humans, who are 'rational beings', have the intrinsic right to be considered as ends in themselves. If capacity for rational thought is the basis of intrinsic rights, some have questioned whether we are justified in using organs taken

from a nonhuman primate but not those taken from an anencephalic, or severely retarded, human. Philosophic justifications for the prohibition against killing incapacitated humans for such purposes have referenced their memories, if any, their potential to grow and form lasting relationships, their capacity to be mourned for long periods, and the effect that using their organs would have on relationships between humans. Others justify this distinction based on religious or metaphysical notions of the inherent elevation of humans above other creatures. These views are not convincing to many animal rights advocates, however.

Nonhuman primates and pigs. Nonhuman primates are biologically close to humans, and many humans feel an emotional attachment to them. They are a concordant species, and would therefore be easier to use as sources for xenotransplantation (from an immunological and physiological perspective) than pigs, which are a discordant species. However, there are several arguments against using them for such purposes. First, the microorganisms they harbour may more easily infect and be pathogenic in humans than would be the case with pigs. Humans have a long history of contact with the pig and the resultant physical proximity has only rarely led to the acquisition of serious infections. Second, it is not possible to raise primates under the husbandry conditions that currently allow for the production of pig herds from which exogenous infectious agents of concern have been excluded (specific-pathogen-free pigs). Third, some primate species (e.g. the chimpanzee) are endangered. While the baboon exists in large numbers and is considered a pest in some parts of the world, it breeds slowly (and it is currently impossible to rear specific-pathogen-free baboons). Thus, a consensus to exclude nonhuman primates as source animals for xenotransplantation has emerged.

There are laws to protect research animals in many countries. Sensible guidelines include the 3 Rs of Russell and Burch (1959) – namely to 'reduce, replace, and refine' – to which we might now add 'respect and reconsider'. There are increased efforts underway to look for alternatives to animal use.

Genetic manipulation of animals for human purposes. The recently acquired power to manipulate the genomes of animals, including the ability to produce 'double knock-outs' and to clone these over several generations raises an important ethical question: Where do we draw the line? The Kennedy Report (1997) and other similar reports have concluded that the current extent of manipulating the pig's genome to incorporate human genes or other manipulations of the same magnitude raise little ethical concern provided the pig 'recognizably remains a pig.' Today, on balance, a case has been made that it is ethically acceptable to use pig organs, but not organs from nonhuman primates, for human xenotransplantation. At this stage of development a larger consensus exists on the importance of attending to 'animal welfare' than to 'animal rights'.

Religious perspectives on xenotransplantation. The views of different religions concerning xenotransplantation largely depend on the manner in which these religions consider animals and how they should be treated. From the religious perspective, it would be important that a xenotransplant not tamper with the human personality or the individual's freedom, and ability, and eligibility to bear responsibility. Minimally, all religions consider that humans have stewardship responsibilities to minimize the pain and suffering of animals being used for the benefit of humans.

Within the three major monotheistic religions (Judaism, Christianity and Islam), human beings have canonically been considered unique, with the rest of creation existing to serve humankind. The Old Testament, the first five chapters of which are canonical to both Jews and Christians, declares: 'Man was made in God's image and has dominion over all other creatures and all the earth.' (Genesis 1:26). In both Judaism and Islam the imperative to preserve human life overcomes many religious prohibitions.

The pig is considered to be ritually unclean in both Islam and Judaism, and it is not surprising that authorities in these two religions have been

asked if the pig can be used as a source animal for organs. In Islam, the conclusion of the majority seems to be that this would not be a barrier to xenotransplantation, based on the Shariah principle that need and necessity can allow that which is forbidden – and that, in any case, the prohibition is only from eating pig tissue. Scholars of Judaism have come to a similar conclusion (Rosner, 1999). There is, however, a minority opinion in Islam that pigs, because they are ritually unclean, cannot be used as source animals.

A number of thoughtful Christian commentators have written about xenotransplantation. On the whole, these are generally accepting, while emphasizing that animal suffering should be minimized. The Catholic Church addressed xenotransplantation as far back as 1956, and in 2000 Pope John Paul II restated its permissive position:[1]

> It is not my intention to explore in detail the problems connected with this form of intervention. I would merely recall that already in 1956 Pope Pius XII raised the question of their legitimacy. He did so when commenting on the scientific possibility, then being presaged, of transplanting animal corneas to humans. His response is still enlightening for us today: in principle, he stated, for a xenotransplant to be licit, the transplanted organ must not impair the integrity of the psychological or genetic identity of the person receiving it; and there must also be a proven biological possibility that the transplant will be successful and will not expose the recipient to inordinate risk.

Some Christian arguments against xenotransplantation have focused on the themes of 'playing God' and 'interfering with creation'. These arguments have less emphasis in Judaism and Islam.

Hinduism, Buddhism and some Animist traditions have not drawn such a sharp theological distinction between humans and other animals, seeing all as part of a hierarchy of creatures, with indistinct borders between them. Other religions supportive of xenotransplantation include Baha'i and Sikhism. Those that have religious concerns about xenotransplantation include Buddhism, Hinduism and Native American faiths (Council of Europe).

Regulatory challenges. The uncertain potential for introducing xenogeneic pathogens has influenced many countries to develop specific policies that incorporate very stringent safety standards for clinical xenotransplantation. Some countries have initiated moratoria, while others have allowed limited and tightly monitored clinical trials. Several countries have developed policies that advocate caution with xenotransplantation clinical trials, requiring that they occur only with regulatory oversight and involve stringent standards for animal husbandry, particularly for screening and surveillance for infectious diseases (Bloom, 2001; Tibbel, 2001; OECD, 2000).

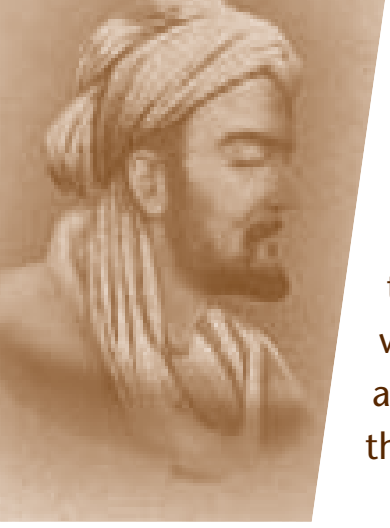
The Council of Europe, the European Agency for Evaluation of Medicinal Products, and the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA, 2003) are developing specific policies on at least certain kinds of xenotransplants that incorporate the concepts of safety built around pre-xenotransplantation screening to prevent transmission of infection and post-transplantation surveillance to maximize the probability of early recognition and containment of any infections introduced through xenotransplantation. Further, the European Union has advocated multinational efforts towards consensus development and collaborative work to minimize threats from emerging infections in general.

Multinational organizations have recognized infectious disease issues associated with xenotransplantation as policy issues that transcend national boundaries. The World Health Organization (WHO) has produced recommendations for addressing and harmonizing issues related to infection control, monitoring, sharing of scientific information, consent and human rights. Both the WHO and the Organization for Economic Co-operation and Development (OECD) have recommended that member states develop regulatory frameworks for xenotransplantation clinical trials, and they have taken leadership roles that encourage international collaborative efforts to minimize infectious risks and actively discourage expatriate xenotransplantation experiments in countries with poor regulatory environments.

Some professional societies were early critics of efforts to bring xenotransplantation clinical trials under special regulatory oversight. In recent years, however, most professional societies have been active advocates for clinical trials under regulatory oversight with stringent husbandry and infection surveillance standards. Many professionals working in xenotransplantation are concerned about 'xenotourism' (the migration of patients across geopolitical boundaries to obtain unregulated xenotransplantation 'therapies'). These patients may undergo risky procedures without adequate understanding, and they may bring unrecognized infections back to their home communities. Further, professionals who conduct expatriate xenotransplantation clinical trials potentially endanger the ability of the field to move forward in a systematic way. In an effort to discourage such practices, the International Xenotransplantation Society has adopted a rule that reports of such experiments will not be accepted for presentation at its meetings or for publication in its journals.

Managing potential conflicts of interest. The increasing participation of private interests in biomedical research is an important trend. One of the key catalysts of this change in the United States was the passage in 1980 of the Bayh-Dole act, which transferred intellectual property rights to researchers funded by federal research monies. In addition, universities in many countries must now attract more private funding to function in a very competitive environment. As a result, companies and investigators with potential conflicts of interest (COI) are testing increasingly powerful experimental therapeutic interventions.

Identifying ways to deal with potential COI while introducing innovative therapies is a complex issue and a constant source of ethical tension. Many would argue that full disclosure of financial and other COI by both institutions and investigators is adequate to manage such COI. Others have argued that disclosure alone may not suffice, and that even a pilot trial should not be conducted if an institution has a major financial



interest in the outcome (Emanuel and Steiner, 1995). The Institute of Medicine has observed, 'Clinical trials with cellular xenotransplants are already under way, and a real danger exists that the commercial applications of xenotransplant technology will outstrip both the research base and the national capacity to address special issues raised by xenotransplantation, including the risk of disease transmission.' (Executive Summary, p. 4)

Timing of clinical introduction of xenotransplantation of whole organs. Although small-scale experimental clinical xenotransplantation of cells and xenotransplantation involving *ex vivo* contact of human living cells with living nonhuman animal cells is underway in some countries, the question of when it would be prudent to translate laboratory successes into clinical trials remains open. The accepted standard is that, before clinical trials are attempted in humans, preclinical research should provide proof of the principle hypothesis adequate to anticipate that humans may benefit from the experiment. However, no consensus has been reached on what would constitute adequate graft survival in animal experiments to justify clinical trials. Attempts to define this crucial criterion have ranged from a median survival time of a minimum of three months to the suggestion that, although it is likely that hyperacute rejection can be prevented, xenotransplants should be delayed until there is a better understanding of acute vascular and cellular responses (Cooper et al., 2000).

Epidemiological surveillance and post-transplant patient monitoring. In the past, infections transferred across species boundaries (e.g. HIV-AIDS, parvoviruses, SARS coronavirus) have spread globally. The development of international surveillance for xenotransplantation-associated infections has been proposed as a way to assist countries to manage risks associated with infections introduced through xenotransplantation performed within and beyond their borders (Ronchi, 2001). Such recommendations raise concerns for many people. The concept of lifelong international surveillance of xenotransplant recipients is fraught with ethical complexities. International

consensus has not been achieved on the definition of xenotransplantation, on what constitutes a xenogeneic infection or disease, on what events should be reported and by what methods, or on which individuals should constitute the population under surveillance. Whether a surveillance system should only report transmission of xenogeneic infections from recipients to their contacts, or should go further to collect information on the contacts themselves, is a source of controversy. All proposed national policies for monitoring xenotransplantation recipients are intrusive. Most advise against unprotected sex, donation of blood or other biological materials, and for education of intimate contacts. Some go further to require the consent of intimate partners for xenotransplantation, active surveillance of intimate contacts as well as xenotransplant recipients, and pre-transplantation agreements to avoid procreation post-xenotransplantation.

Patient–physician relationships and consent. The perceived potential for xenotransplantation to benefit an individual while putting the larger community at risk complicates both the patient-physician relationship and the issue of informed consent. The Helsinki Declaration on Ethical Principles for Medical Research Involving Human Subjects states that, in medical research on human subjects, considerations related to the well being of the human subject should take precedence over the interests of science and society. Xenotransplantation clinical trials present situations that may place the interests of recipients and the greater good of society at odds. If a doctor is required to think of the public interest rather than merely the interests of the immediate patient, the traditional role of the physician as patient advocate is altered. At best, this will create confusion, since the physicians must weigh the responsibility to individual patients against the public good. At worst, the doctor-patient relationship itself could become one of antagonism rather than of trust (Daar, 1997).

The current informed-consent requirements for patients who might receive xenotransplants exceed those required in most other research settings. A major question on which there is

no consensus at present is the problem of what to do if a patient changes her or his mind about intrusive follow-up monitoring and the waiver or curtailment of confidentiality rights previously agreed to. Informed consent is not usually legally binding on the patient, who retains a right to withdraw participation at any point in the investigational process.

Given the expectations of lifelong follow-up for initial xenotransplant recipients, a different kind of consent has been discussed (Daar, 1999). A specific legal contract might provide enforceability of pre-transplant agreements for lifelong monitoring. Unlike the traditional consent form, such a contract would allow specific curtailment of the patient's rights. (The traditional consent procedure does not, in all cases, require that a document be signed; more often than not, the signed form protects the doctor more than the patient.) Such a legal contract would be a radical departure from current accepted norms, since it would directly conflict with the present emphasis on the primacy of respect for the autonomy of the research subject. Thus, these issues are fraught with controversy.

Models to build on. Are there any precedents in which a patient can decide in advance what medical treatment she or he would want to receive in the future? Both 'advance directives' and the so-called 'Ulysses contract' fall into this category.

Advance directives are used in medicine as a means by which patients declare their wishes in anticipation of a future day when they may not be competent to make decisions. Such an instrument has been used, for example, to establish the point at which a patient desires a 'do not resuscitate' status. It could be adapted to allow a mentally competent xenotransplantation recipient to make provision for intrusive post-transplant medical monitoring (with its attendant curtailment of certain rights) to continue if the recipient changes her or his mind – a situation that might occur if, for example, the graft fails but monitoring must continue in order to protect public health.

This would be more akin to a 'Ulysses contract'. In Greek mythology, Ulysses was a strong, good man. He knew he would sail near the Sirens whose enchanting songs would overcome him and cause his ship to be destroyed. He ordered his sailors to plug their ears and, wanting to hear the songs, had himself tied to the mast of the ship, ordering his companions not to release him regardless of his subsequent demands. A Ulysses contract, then, is used for patients who are likely to experience periods of incompetence in the future, such as patients with psychiatric disorders characterized by alternating periods of therapy-induced competence and incompetence. While they are in a competent state, they can specify treatment decisions for future occasions. In the xenotransplant setting, such a binding advance directive signed by the recipient prior to the xenotransplantation could, theoretically, be used to forcibly investigate, treat, or even confine a recipient who fails to meet responsibilities to the public agreed to prior to the procedure (Daar, 1999). A Ulysses contract usually assumes that the subject is so affected as to have their 'true' judgement subordinated by some other pressure, while in this instance the xenotransplantation recipient may merely have changed her or his mind about cooperating with intrusive surveillance. Discussion of these options has raised concerns about the possibility of unacceptably eroding the human rights of research participants on the basis of hypothesis and fear rather than established or proximate risk.

Public engagement and public consent. Some people have argued that since the public is going to be exposed to some level of risk of xenogeneic infections, the public must be consulted, and must consent, before xenotransplantation clinical trials proceed. Many national reports recommend that the public must in some way be consulted before proceeding with xenotransplantation. It is, however, difficult to define what would constitute 'public consent'. Further, efforts at public education can easily merge over into propaganda, since the opinions formed by non-experts are completely dependent on the nature and presentation of the information they receive.

While some have advocated a moratorium pending public consent (Bach et al., 1998) there are significant problems with adopting a moratorium. The majority of researchers and clinicians appear to be opposed to this position, mainly because moratoria remove from public discourse the very issues that ought to be addressed. Most researchers and clinicians would encourage increased capacity to evaluate the potential social consequences as the technology develops. Significantly, there have been no serious calls for reduction in xenotransplantation research.

Canada has undertaken a major public engagement exercise consisting of a series of forums involving education, discussion and 'citizen juries'. A subsequent report of the Canadian Public Health Association has recommended that Canada not proceed with xenotransplantation involving humans until several critical issues are addressed. It recommends, among other steps, that further efforts be made to inform and educate the public; that additional preclinical research be carried out; and that the risks and probability of benefit from clinical trials be more fully defined. It also calls for the development of legislation and regulations to cover all aspects of xenotransplantation clinical trials, concluding that there is a continuing need to involve the public in discussions about the future of xenotransplantation. This approach, however, has been criticized as being vulnerable to biases introduced by the information presented to the public (Wright, 2002). Nevertheless, this particular exercise reflects the current uncertainties surrounding xenotransplantation.

Conclusion

Xenotransplantation currently describes a multifaceted array of experimental biotechnological approaches to disease amelioration, some of which have progressed to small-scale clinical trials. The theoretical risk of infections spreading from source animal to recipient and then to contacts and the public has triggered debates on issues of science and on how biomedical

technology should be developed, regulated and implemented. The specific ethical dilemmas discussed in the context of xenotransplantation reflect areas of ethical conflict and uncertainty relevant to other aspects of community life. These include the rights of the minority in the face of concern by the majority; conflicting values around decision-making in the face of uncertain collective risk; the relative rights of humans and nonhuman animals; the relative value of safety versus of hope for progress; and the rights of, and appropriate protections afforded to, human subjects of research.

Note

1. Transplantation Society. 2000. Address of Pope John Paul II to the 18th International Congress of the Transplantation Society. http://cnserver0.nkf.med.ualberta.ca/misc/Rome/Encyclical.htm (Accessed 10 February 2006.)

References

Advisory Group on the Ethics of Xenotransplantation. 1997. *Kennedy Report: Advisory Group on the Ethics of Xenotransplantation: Animal Tissues into Humans.* HM Stationery Office, London.

Auchincloss, H., Jr. 2001. In Search of the elusive Holy Grail: The mechanisms and prospects for achieving clinical transplantation tolerance. *American Journal of Transplantation*, Vol. 1, No. 1, pp. 6-12.

Bach, F. H., Fishman, J. A., Daniels, N., Proimos, J. et al. 1998. Uncertainty in xenotransplantation: Individual benefit versus collective risk. *Nature Medicine*, Vol. 4, No. 2, pp. 141-144.

BBC News. 2003. Ape 'Learns to Talk'. http://news.bbc.co.uk/1/hi/sci/tech/2617063.stm (Accessed 10 February 2006.)

Bentham, J. 1789. *An Introduction to the Principles of Morals and Legislation.* Reissued by Prometheus Books, Amherst, NY.

Bloom, E. T. 2001. Regulating xenotransplantation in the United States. *Graft*, Vol. 4, No. 2, pp. 160-162.

Canadian Public Health Association. 2001. *Animal-to-Human Transplantation: Should Canada Proceed?* http://www.xeno.cpha.ca (Accessed 10 February 2006.)

Centers for Disease Control and Prevention (CDC). 1998. CDC Update: Isolation of Avian Influenza A(H5N1) Viruses from Humans – Hong Kong, 1997-1998. *Morbidity and Mortality Weekly Report*, Vol. 46,

No. 52, pp. 1245-1247. http://www.cdc.gov/mmwr/PDF/wk/mm4652.pdf (Accessed 10 February 2006.)

_____. 1999. CDC Update: Outbreak of Nipah Virus – Malaysia and Singapore, 1999. *Morbidity and Mortality Weekly Report*, Vol. 48, No. 16, pp. 325-348. http://www.cdc.gov/mmwr/PDF/wk/mm4816.pdf (Accessed 10 February 2006.)

_____. 2001. U.S. Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation. *MMWR Recommendations and Reports*, August 24, 2001/50(RR15), pp. 1-46. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5015a1.htm (Accessed 10 February 2006.)

Chapman, L.E., Folks, T. M., Salomon, D. R., Patterson, A.P. et al. 1995. Xenotransplantation and Xenogeneic Infections. *New England Journal of Medicine*, Vol. 333, No. 22, pp. 1498-1501.

Chari, R. S. et al. 1994. Treatment of Hepatic Failure with Ex Vivo Pig-Liver Perfusion followed by Liver Transplantation. *New England Journal of Medicine*, Vol. 331, No. 4, pp. 234-237.

Church of Scotland, Society, Religion and Technology Project. 1995. The Ethics of Xenotransplantation. http://www.srtp.org.uk/xennuf03.shtml#Contents (Accessed 10 February 2006.)

Collins, B. H., Parker, W. R. and Platt, J. L. 1994. Characterization of Porcine Endothelial Cell Determinants Recognized by Human Natural Antibodies. *Xenotransplantation*, Vol. 1, p. 36.

Cooper, D. K., Keogh, A. M., Brink, J., Corris, P. A. et al. 2000. Report of the Xenotransplantation Advisory Committee of the International Society for Heart and Lung Transplantation: The Present Status of Xenotransplantation and Its Potential Role in the Treatment of End-Stage Cardiac and Pulmonary Diseases. *Journal of Heart and Lung Transplantation*, Vol. 19, No. 12, pp. 1125-1165.

Council of Europe Working Party on Xenotransplantation. 2003. Report on the State of the Art in the Field of Xenotransplantation. http://www.coe.int (Accessed 10 February 2006.)

Cozzi, E., Tucker, A. W., Langford, G. A., Pino-Chavez, G. et al. 1997. Characterization of Pigs Transgenic for Human Decay-Accelerating Factor. *Transplantation*, Vol. 64, No. 10, pp. 1383–1392.

Daar, A. S. 1994. Xenotransplantation and Religion: The Major Monotheistic Religions. Xenotransplantation, Vol. 2, pp. 61-64.

_____. 1997. Ethics of Xenotransplantation: Animal Issues, Consent, and Likely Transformation of Transplant Ethics. *World Journal of Surgery*, Vol. 21, pp. 975-982.

_____. 1999. Xenotransplantation: Informed Consent/Contract and Patient Surveillance. *Biomedical Ethics*, Vol. 4, No. 3, pp. 87-91.

_____. 2001. Choosing Risk-Benefit Analysis or Precautionary Principle as Our Approach to Clinical Xenotransplantation. *Graft*, Vol. 4, No. 2, pp. 164-166.

Diamond, L.E., McCurry, K. R., Martin, M. J., McClellan, S. B. et al. 1996. Characterization of Transgenic Pigs Expressing Functionally Active Human CD59 on Cardiac Endothelium. *Transplantation*, Vol. 61, pp. 1241-1249.

Diamond, L. E., Quinn, C. M., Martin, M. J., Lawson, J. et al. 2001. A Human CD46 Transgenic Pig Model System for the Study of Discordant Xenotransplantation. *Transplantation*, Vol. 71, pp. 132-142.

Dossetor, J. B. and Daar, A. S. 2001. Ethics of Transplantation: Allotransplantation and Xenotransplantation. *Kidney Transplantation:Principles and Practice*, 5th edn, P. J. Morris (ed.). Philadelphia, W. B. Saunders.

Emanuel, E. J. and Steiner, D. 1995. Sounding Board: Institutional Conflict of Interest. *New England Journal of Medicine*, Vol. 332, No. 4, pp. 262-268.

Fink, J. S. et al. 2000. Porcine Xenografts in Parkinson's Disease and Huntington's Disease Patients: Preliminary Results. *Cell Transplantation*, Vol. 9, pp. 273-278.

Fishman, J. A. 2001. Infection in Xenotransplantation. *Journal of Cardiac Surgery*, Vol. 16, No. 5, pp. 363-373.

Goklany, I. M. 2002. From Precautionary Principle to Risk–Risk Analysis. *Nature Biotechnology*, Vol. 20, No. 11, p. 1075.

Hahn, B. H., Shaw, G. M., De Cock, K. M. and Sharp, P. M. 2000. AIDS as a Zoonosis: Scientific and Public Health Implications. *Science*, Vol. 287, No. 5453, pp. 607-614.

Hammer, C. and Thein, E. 2001. Physiological Aspects of Xenotransplantation. *Xenotransplantation*, Vol. 9, pp. 303-305.

Heneine, W., Tibell, A, Switzer, W. M. et al. 1998. No Evidence of Infection with Porcine Endogenous Retrovirus in Recipients of Porcine Islet-Cell Xenografts. *Lancet*, Vol. 352, pp. 695-699.

Ivinson, A. J. 1998. Does Biomedical Research Need Another Moratorium? *Nature Medicine*, Vol. 4, No. 2, p. 131.

Institute of Medicine. 1996. *Xenotransplantation: Science, Ethics, and Public Policy.* Washington, D.C., National Academy Press.

Levinsky, N. G. 2002. Nonfinancial Conflicts of Interest in Research. *New England Journal of Medicine*, Vol. 347, No. 10, pp. 759-761.

Michaels, M. G. 2001. Determining the Risk of Xenozoonoses. *Graft*, Vol. 4, No. 2, pp. 129-130.

Moosa, M. R., Walele, A. A. and Daar, A. S. 2001. Renal Transplantation in Developing Countries. *Kidney Transplantation: Principles and Practice*, 5th edn, P. J. Morris (ed.). Philadelphia, W. B. Saunders.

Nuffield Council on Bioethics. 1996. Animal-to-Human Transplants: The Ethics of Xenotransplantation. London, Nuffield Council on Bioethics. http://www.nuffieldbioethics.org (Accessed 10 February 2006.)

Organization of Economic Co-operation and Development (OECD). Joint WHO/OECD Consultation on Xenotransplantation Surveillance, 4-6 October 2000. http://www.oecd.org (Accessed 10 February 2006.)

O'Riordan, T. and Jordan, A. 1995. The Precautionary Principle in Contemporary Environmental Politics. *Environmental Values*, Vol. 4, p. 191.

Paradis, K., Langford, G., Long, Z., Heneine, W. et al. 1999. Search for Cross-Species Transmission of Porcine Endogenous Retrovirus in Patients Treated with Living Pig Tissue. *Science*, Vol. 285, pp. 1236-1241.

Patience, C., Patton, G. S., Takeuchi, Y., Weiss, R. A. et al. 1998. No Evidence of Pig DNA or Retroviral Infection in Patients with Short-Term Extracorporeal Connection to Pig Kidneys. *Lancet*, Vol. 352, pp. 699-701.

Patience, C., Takeuchi, Y. and Weiss, R. A. 1997. Infection of Human Cells By an Endogenous Retrovirus of Pigs. *Nature Medicine*, Vol. 3, pp, 276-282.

Phelps, C. J., Koike, C., Vaught, T. D., Boone, J. et al. 2003. Production of Alpha1, 3-Galactosyltransferase-Deficient Pigs. *Science*, Vol. 299, pp. 411-414.

Pitkin Z. and Mullon, C. 1999. Evidence of Absence of Porcine Endogenous Retrovirus (PERV) Infection in Patients Treated with a Bioartificial Liver System. *Artificial Organs*, Vol. 23, No. 9, pp. 829-833.

Regan, T. 1983. *The Case for Animal Rights*. Los Angeles, University of California Press.

Ronchi, E. 2001. OECD/WHO Consultation on Xenotransplantation Surveillance: Summary Report. Directorate for Science, Technology and Industry – Committee for Scientific and Technological Policy, Working Party on Biotechnology. http://www.olis.oecd.org/olis/2001doc.nsf (Accessed 10 February 2006.)

Rosner, F. 1999. Pig Organs for Transplantation into Humans: A Jewish View. *Mount Sinai Journal of Medicine*, Vol. 66, Nos 5-6, pp. 314-319.

Russel, W. M. S. and Burch, R. L. 1959. *The Principles of Humane Experimental Technique*. London, Methuen.

Sandrin, M. S., Fodor, W. L., Mouhtouris, E., Osman, N. et al. 1995. Enzymatic Remodeling of the Carbohydrate Surface of a Xenogenic Cell Substantially Reduces Human Antibody Binding and Complement-Mediated Cytolysis. *Nature Medicine*, Vol. 1, pp. 1261-1267.

Sandrin, M. S., Vaughan, H. A., Dabkowski, P. L. and McKenzie, I. F. C. 1993. Anti-Pig IgM Antibodies in Human Serum React Predominatly with Gal (1,3) Gal Epitopes. *Proceedings of the National Academy of Science USA*, Vol. 90, p. 11391.

Saner, M. A. 2002. An Ethical Analysis of the Precautionary Principle. *International Journal of Biotechnology*, Vol. 4, No. 1, pp. 81–95.

Schumacher, J. M., Ellias, S. A. et al. 2000. Transplantation of Embryonic Porcine Mesencephalic Tissue in Patients with PD. *Neurology*, Vol. 54, No. 5, pp. 1042-1050.

Sharma, A., Okabe, J., Birch, P., McClellan, S. B. et al. 1996. Reduction in the Level of Galalpha(1,3)Gal in Transgenic Mice and Pigs by the Expression of an Alpha(1,2) Fucosyltransferase. *Proceedings of the National Academy of Sciences USA*, Vol. 93, pp. 7190-7195.

Shiraishi, M., Oshiro, T., Nozato, E., Nagahama, M. et al. 2002. Adenovirus-Mediated Gene Transfer of Triple Human Complement Regulating Proteins (DAF, MCP and CD59) in the Xenogeneic Porcine-to-Human Transplantation Model. *Transplant International*, Vol. 15, No. 5, pp. 212-219.

Singer, P. 1975. *Animal Liberation*. New York, Random House.

Soares, M. P., Brouard, S., Smith, R. N. and Bach, F. H. 2001. Heme Oxygenase-1, a Protective Gene That Prevents the Rejection of Transplanted Organs. *Immunological Reviews*, Vol. 184, pp. 275-285.

Stoye, J. P. 1998. No Clear Answers on Safety of Pigs As Tissue Donor Source. *Lancet*, Vol. 352, No. 9129, pp. 666-668.

Swedish Committee on Xenotransplantation. 1999. *From One Species to Another: Transplantation from Animals to Humans*. Swedish Government Official Report No. 1999: 120.

Tearle, R. G., Tange, M. J., Zanettino, Z. L. et al. 1996. The -1,3-Galactosyltransferase Knockout Mouse: Implications for Xenotransplantation. *Transplantation*, Vol. 61, p. 13.

Tibbel, A. 2001. Regulating Xenotransplantation in Europe. *Graft*, Vol. 4, No. 2, pp. 157-159.

United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA). Draft guidance notes on biosecurity considerations in relation to xenotransplantation. http://www. advisorybodies.doh.gov.uk/ukxira/publications.htm (Accessed 10 February 2006.)

U.S. Food and Drug Administration. 1999. Guidance for Industry; Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans. http://www.fda.gov/cber/gdlns/xenoprim.pdf (Accessed 10 February 2006.)

van der Laan, J. W., Lockey, C., Griffeth, B. C., Frasier, F. S. et al. 2000. Infection by Porcine Endogenous Retrovirus after Islet Xenotransplantation in SCID Mice. *Nature*, Vol. 407, pp. 90-94.

White, D. and Wallwork, J. 1993. Xenografting: Probability, Possibility, or Pipe Dream? Lancet, Vol. 342, p. 879.

Wilson, C. A., Wong, S., Muller, J., Davidson, C. E. et al. 1998. Type C Retrovirus Released from Porcine Primary Peripheral Blood Mononuclear Cells Infects Human Cells. *Journal of Virology*, Vol. 72, pp. 3082-3087.

World Health Organization (WHO). 1997. *Report of the WHO Consultation on Xenotransplantation*. Doc. No. WHO/EMC/ZOO/98.2. Geneva, Switzerland, World Health Organization. http://whqlibdoc.who.int/hq/1998/WHO_EMC_ZOO_98.2.pdf (Accessed 10 February 2006.)

Wright, J. R., Jr. 2002. Alternative Interpretations of the Same Data: Flaws in the Process of Consulting the Canadian Public about Xenotransplantation Issues. *Canadian Medical Association Journal*, Vol. 167, pp. 40-42.

Wu, A., Yamada, K., Neville, D. M., Awwad, M. et al. 2003. Xenogeneic Thymus Transplantation in a Pig-to-Baboon Model. *Transplantation*, Vol. 75, No. 3, pp. 282-291.

Chapter 6

Abdallah S. Daar

*Regenerative Medicine: A taxonomy for addressing ethical, legal and social issues**

The population of the world is aging. The process is far advanced in developed countries but even the populations of many developing countries are experiencing a demographic shift. Degenerative diseases such as Alzheimer's disease, Parkinson's disease and various forms of arthritis are imposing greater burdens on health care systems, as are metabolic diseases such as diabetes, which lead in turn to organ failure.

Traditional organ transplantation addresses end-stage organ failure, both of solid organs such as the kidney, the liver and the heart, and tissues such as bone marrow, based on cellular therapy. Tissue replacement, on the other hand, deals with heart valves, joints, bones and skin where these are needed for replacement. In North America, tissue replacement is catered for mainly by tissue banking commercial organizations that collect from

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cadavers the needed tissues. These two domains of activity use what is largely already available from other human sources without any further significant biomedical interventions. There is little application, apart from preservation techniques, of any molecular-level science.

The emerging discipline of regenerative medicine (RM) goes further than the above. The contours of the field of RM are still being defined. One major focus is tissue engineering, which seeks to engineer completely new tissue, and in this endeavour it uses living cells, biodegradable materials and soluble factors (e.g. growth factors) to build tissues of varying degrees of structural complexity. In its wildest dreams, RM hopes to build 'off-the-shelf' organs (Atkins and Sefton, 2001; Sefton, 2002), so that one day anyone with a massive heart attack, say, will be able to receive a ready-made heart, and ideally this will not be rejected by the body's immune system. We are a long way away from that. We still need to identify the best scaffolds for different tissue constructs. We need to learn much more about how such tissue constructs interact with the recipient's own tissues. We need to learn how the new tissues will integrate both structurally and functionally, how they will be accepted by the immune system, and how they will respond to normal biological signals, including hormones and nerve impulses. Researchers are working hard to develop techniques to stimulate neo-vascularization and formation of fine capillary beds, and the fine imaging that is needed to see what is happening at minute levels. Different biomaterials, including composites, are being tried for different functions. Other emerging technology platforms, such as nanotechnology, are being recruited to enable RM. Stem cells and even genetic engineering will likely play major roles in the future of RM – both these are, of course, surrounded by ethical controversy (Daar and Sheremata, 2002).

Conceptually what is really exciting is the exploration not of replacement technologies but of repair technologies, where the body will be encouraged to repair its own damaged tissue. An exciting, and increasingly realistic, prospect is spinal cord regeneration. There are promising new laboratory

models involving neurotropic factors, stem cells, olfactory sheath cells, and tiny tubes that guide regenerating nerve tissue.

William Haseltine observes that the key insights of regenerative medicine is that every human being was once a single cell with the potential to transform into an adult body; and each of our cells retains that remarkable potential in a latent form. We have over the past decade learned how to identify the molecules that our bodies use to direct that great unfolding. We can now isolate, study, and produce those substances in virtually unlimited quantities and use them to regenerate our tissues and organs (Haseltine, 2001).

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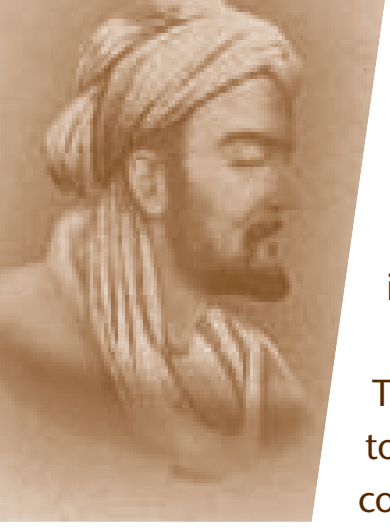
At one level, what is really important is to get a complete understanding of how the cell functions. One of the emerging institutes dedicated to regenerative medicine aims to discover the basic principles underlying how cells form, organize, maintain, regenerate, and repair the proper three-dimensional structures of tissues and organs.[1] Other institutes have wider objectives: one aims to provide a national centre of expertise in regenerative medicine focused on developing and delivering therapies that re-establish tissue and organ function impaired by disease, trauma or congenital abnormalities.[2]

Unlike the origins of traditional organ transplantation, RM is developing at a time when many academics are working with, or moving into, industry on a large scale. Some of the world's largest biotechnology companies are involved in various aspects of RM. The tissue engineering industry has grown phenomenally recently. There are now many start-up companies engaged in RM research and development in the USA and Europe, employing thousands of scientists and support staff. Spending by tissue engineering firms has been growing at a compound annual rate of 16%, and the aggregate investment since 1990 now exceeds $3.5 billion. The number of companies involved in stem cells and regenerative medicine is rapidly increasing, and this area represents the most likely nidus of future growth for tissue engineering (Lysaght and Reyes, 2001). In industry one of the



key assets that new companies have is 'intellectual property', of which the most familiar is a patent. Intellectual property is surrounded by misunderstandings and misinterpretations, and is ripe for serious academic scholarship (Gold et al., 2002).

There is now a new journal dedicated to RM[3], which happens to be edited by William Haseltine, who not only is credited with coining the term 'Regenerative Medicine' but also heads Human Genome Sciences Inc.[4], which is one of the largest biotechnology companies in the world and a pioneer in RM research. His own history of moving from academia to industry is emblematic of the new age of biotechnology start-up companies formed rapidly from scientific breakthroughs and intellectual property created by academics.

In summary, while the contours of this new super-discipline are still being defined and the definition of RM can be either narrow or very wide, the field is generally about *replacement*, *repair* and *regeneration* to address deficient organ function resulting from congenital defects, disease, trauma or wear and tear. Other Rs that perhaps help to describe the field include recover, restore and remodel.

Timelines of the vision

At present we are on the threshold of using human molecules to stimulate the repair and restoration of natural bodily functions: osteogenic and vasculogenic factors will likely be in clinical trial or use within about a decade. Implanting tissues and organs grown outside the body by treating stem cells with human signalling molecules will likely follow in the next decade. After that we may be able to reset the genetic clock within cells, making possible the rejuvenation of aging tissues. It is believed that such practical implications will be seen within 30 years. It may one day be possible to use nanotechnology to create artificial materials that will integrate seamlessly with our natural ones. The ultimate goal is neuro-

mechanical prostheses that will respond smoothly and precisely to neural and other biological impulses (Haseltine, 2001).

Taxonomy

It is perhaps too early to arrive at a definitive taxonomy that will encompass all possible ethical, legal and social issues that may arise. However, it is possible to devise a taxonomy based on experience with organ transplantation and on experience with introduction of new technologies generally (Box 1). Addressing these issues in a constructive way will enable this emerging field to progress rapidly (since the need for it is enormous already and is growing rapidly, and there may be indications for various forms of RM that we have not yet imagined

Box 1 | RM Ethical, Legal and Social Implications (RM-ELSI): An early taxonomy

1. Issues related to transplantation
   - Allotransplantation
   - Xenotransplantation
2. Issues related to introduction of new technologies
   - Regulation (safety, quality control, etc.)
   - Intellectual property
   - Management of innovation
   - Innovation vs. research paradigms
   - Conflict of interest
   - Commercialization
   - Equity
   - Priority setting/resource allocation
3. Issues related to enabling technologies
   - Nanotechnology
   - Stem cells
   - Genetic engineering
4. Issues related to applications
   - Normality and enhancement
   - Neuroethics
5. Issue related to public engagement
   - Cultural issues
   - Civil society bodies

today) while we minimize or manage any associated risks and uphold generally accepted societal values.

Issues related to organ transplantation

The major issue has always been organ shortage and the subsidiary concerns that this has raised, including payments for organ procurement, 'unconventional' methods of increasing organ availability such as non-heart-beating donation, presumed consent, etc. (Dossetor and Daar, 2001). In addition, since it is possible that nonhuman animal cells, tissues or soluble products may be needed to facilitate RM, all the issues related to xenotransplantation will need to be considered. For example, human embryonic stem cells need to be grown at some stage on a bed of murine feeder cells (this may change as it is now becoming possible to grow them without this) and by strict definition this makes the stem cells xenogeneic material which requires a different set of regulations. These at present are mainly related to the unknown risk of xenogeneic infections such as porcine endogenous retroviruses and the management of this risk in terms of safety precautions before and after transplantation. Another set of issues is related to animal welfare and religious considerations. We have recently reviewed the ethical, legal and social issues of xenotransplantation (Daar and Chapman, 2004).

Issues related to introduction of new technologies

Any new technology, technology platform or series of technologies involved in establishing a new modality of intervention (RM falls in this category) is bound to have its own set of risks. These in turn raise a number of societal concerns and, generally speaking, it could be said that the more powerful the technologies, the more issues it raises – especially if the science is evolving very rapidly and clinical introduction is going to be rapid; these are all conditions that apply to RM. There is a need to

protect human subjects of research and ensure that any procedures and products are introduced after due deliberation. To gain public support it is important to avoid early pitfalls in the introduction of RM modalities in clinical practice. Questions that will need to be addressed include: Will the development of RM be supported by other disciplines? How can we best assess demand for RM? Will it increase or decrease costs to the health-care system? Are there ways of introducing RM that will minimize negative costs and organizational impacts?

Safety and quality control are paramount, and the involvement of industry adds another dimension, since commercialization of health related products always brings to the fore the essential tension between the need to innovate and the need to ensure that socially useful products are available for the benefit of all – hence the complicated, confusing and vexing discourse that surrounds intellectual property. The rights to control the use and dissemination of RM innovation are an important element in a country's ability to encourage an active research and development agenda, to provide the financial stability to industry, and to ensure access to new health technologies. These rights take on several forms, the most prominent of which are patents, copyrights and trade secrets. It is important to understand the intellectual property rules underlying any area of technological development, and this is particularly true of foundational technologies, from stem cells to nanotechnology, that will form the basis of advances in RM for years to come. Many of the IP issues that arise in current biotechnologies (Gold et al., 2002) will be relevant to, and shed light upon, RM. RM technology will likely lead to similar concerns as have arisen from DNA sequence patenting. As the recent decision by the Ontario government to challenge Myriad Genetics on its broad patent over BRCA gene testing for breast cancer illustrates, intellectual property plays a crucial role in assuring both innovation and access to good health care at an affordable cost. The Myriad case highlights the conundrum that countries like Canada face at a time when its own innovation system is also encouraging the development of its own

serious biotechnology industry (Caulfield et al., 2003). If the investment that countries are putting into RM is to pay off not only in improved health care but also in commercialization of RM research, then it is crucial that we examine all issues related to RM commercialization early.

Clinicians and clinician scientists, particularly in surgery, often work in the 'grey zone' between established practice on the one hand, and established research on the other; this is the zone of incremental innovation – maybe small steps that are introduced in techniques that do not yet amount to research as such, the latter of course requiring specific approval by institutional review boards. In this innovation zone, how do you ensure that the human subject/patient is protected and that personal and institutional conflicts of interests are managed appropriately? (McKneally and Daar, 2003)

Finally there is always the issue of equity: Will the new technologies/therapies be available only to the rich few? This is an issue not only for individual countries – we must think globally (Benatar et al., 2003), generally in terms of minimizing huge health disparities but also in terms of avoiding divides related to particular technologies (Singer and Daar, 2001; Mnyusiwalla et al., 2003). In this sense, one of the key issues is how resources are allocated, and the processes of priority setting in institutions, countries and globally (Martin and Singer, 2003). One of the most glaring inequities at a global level, for example, is the disturbing fact that 90% of all health care research dollars are spent on addressing the needs of only 10% of the world's population: the so-called 10:90 gap.

Issues related to enabling technologies

RM is the prototypical application field in which NBIC (the newly coined term refers to the convergence of nanotechnology, biotechnology, information technology and cognitive sciences) is coming to fruition.

Nanotechnology. Nanotechnology will likely be an important enabling set of technologies for RM. Nanotechnology itself has raised a number of important ethical issues that we are only just beginning to address now. There is, for example, already a call for a moratorium on developing new nanotechnology materials. The risks, of course, must be studied very carefully but uninformed media comments must not hinder proper risk evaluation or the conduct of research. It is possible that this emerging technology will be derailed before there has been adequate study of its ethical, economic, environmental, legal and social implications (E3LSI). There is an enlarging gap between scientific research in nanotechnology and the social evaluation of this emerging technology: either the ethics will have to speed up or the science will have to slow down (Mnyusiwalla et al., 2003). Some of the issues that need to be addressed are those involving privacy, security, environment and human-machine interface. There are also several important legal issues (Moore, 2002).

Stem cells. One of the most exciting developments in the biological sciences in the past decade has been the discovery and characterization of human embryonic stem cells (ESCs) (Shamblott et al., 1998) – a discovery that has spurred research into all other types of stem cells and their potential therapeutic applications. Stem cells will very likely feature in a major way in RM. There are already a number of ethical issues that need to be addressed quite seriously, particularly in relation to embryonic stem cells (Daar and Sheremata, 2002).

Research is being carried out not only in the developed, but also in the developing world – China, for example, is one of the world's leading countries in stem cell research and in September 2003 Brazilian researchers showed that bone marrow stem cells, when injected into the left ventricle, can 'heal' the hearts of patients awaiting transplants for heart failure to the extent that they no longer need a transplant[5].

There is little controversy surrounding human adult stem cells. However, ESCs are surrounded by a number of controversies, the extent of which is partly dependent on their source. Current sources are existing embryonic stem cell lines (of which there are fewer than was initially thought); 'excess' embryos from in vitro fertilization (IVF) clinics; IVF embryos specifically created so they can be destroyed for their ESCs; parthenogenetic tissue; and somatic cell nucleus transfer (SCNT). SCNT is controversial because of the questions it raises regarding the beginnings of life and the conflation with the abortion debate – a subject of major interest not only to ethicists, but also to religious and political leaders. A way to approach this subject is through the lens of a moral 'singularity' to focus on the point of transition from an entity that we owe no special moral consideration to (e.g. a somatic cell), to one that we do (the Catholic church for example considers the singularity to occur at conception, Muslims at ensoulment, etc.) (Daar and Sheremata, 2002). However, there are some recent scientific developments that may in the long run reduce or obviate many of the concerns associated with SCNT (Caulfield et al., 2003): for example it may one day be possible to reprogram somatic cells and convert them directly into cells with the functional characteristics of ESCs without even the need for an oocyte.

The regulatory environment in this area, which is linked to embryo research generally, is quite variable. It ranges from the more permissive (e.g. in the United Kingdom, with its Human Embryology and Fertilization Authority that can license such research[6]) to the nominally much more restrictive regime in the United States (nominally in the sense that while federal funds cannot be used for embryo research, private sector money flows into such research freely and the US Congress seems, so far, to be unable to pass legislation that is acceptable to all segments of society – a situation not different from Canada's) to the truly restrictive (Germany) (Caulfield, in press).

Applications

Neuroethics. The convergence of stem cell technologies, genetic manipulation, advanced imaging technologies and a richer understanding of neuroscience will increase our ability to treat a number of common debilitating neurological conditions, including neuro-trauma, by RM. It seems likely that addressing neuro-degenerative diseases such as Parkinson's and Alzheimer's will be a substantive part of RM. These considerations are giving rise to a whole new discipline of 'neuroethics' which is emerging to address the issues that will arise, for example, when we begin seriously to perform neurological implantations. It is also possible that the ethical, legal and social issues here will be more contentious and more immediate than those raised in genetics research (The Economist, 2002). There is also the link to xenotransplantation (Daar and Chapman, 2004): because human fetal tissue is limited by ethical, infectious, regulatory and practical concerns, other mammalian neural tissue is being studied as an alternative therapeutic cell source. Phase I studies of pig fetal neural cells grafted unilaterally into Parkinson's disease and Huntington's disease patients have demonstrated some improvement in symptoms in Parkinson's disease patients (Fink et al., 2000).

RM, normality, therapy and enhancement. These are issues that will face any technology with potential 'dual-use', i.e. that has the potential not only for treating established derangements in anatomy and physiology but that can also be used for enhancement of normality – a subject that has its own baggage of concerns. The following questions are likely to arise as RM gets closer to clinical introduction: 1) Is RM any different from other therapeutic interventions already in use? 2) Can we define what distinguishes RM from other therapies? 3) How do we draw the line between incapacity requiring standard therapy and that requiring RM intervention? 4) Are there different levels of RM interventions that require different levels of concern? 5) Can we develop a taxonomy that clarifies

how we approach these questions such as RM interventions requiring use of embryonic stem cells versus those that do not, RM interventions that require immunosuppression versus those that do not, RM interventions that will clearly raise total health expenditures versus those that will lower expenditures, etc.?

Public engagement

Cultural considerations. Human subjects for RM research and patients receiving RM therapies will inevitably come from different cultural backgrounds. It is important therefore that RM researchers and health-care providers be prepared for these cross-cultural encounters and have guidelines on how to approach sensitive cultural issues that may arise. Organ transplantation provides some lessons (Marshall and Daar, 1998). These issues are particularly sensitive when the heart is involved. The general public considers heart transplantation being nearly miraculous. The heart is considered by some cultures as the seat of life. It has many symbolic attachments. Within some religious traditions life only ends when the heart stops. Some cultural issues may also arise in relation to neural regeneration and transplants.

Stakeholder issues: Voluntary health organizations. In many countries now there are strong civil-society organizations that include voluntary health organizations (VHOs). These are known by several other names such as patient groups, patient advocacy organizations, interest groups, etc. and include in Canada the Muscular Dystrophy Association, the Juvenile Diabetes Research Foundation, the Heart and Stroke Foundation, and so forth. VHOs are likely to play a major role in the unfolding of RM.

VHOs have different histories and origins, different fund-raising capacities, and different ways of achieving their aims in seeking solutions to reduce the

burden of the conditions they represent. Because RM will seek to ameliorate and even try to heal many of the conditions that are of interest to VHOs, it is important to understand how their work will help, hinder, or inform the development of RM both at the research phase and at clinical introduction. The kinds of questions that arise are: 1) How do VHOs affect research direction and what is their role in funding, advocacy and involvement in peer-review processes? and 2) Ought they to have a bigger or smaller role in these spheres and in building research capacity? We need to consider their role in mobilizing people to participate in the policy process as citizens and informing formal and informal coalitions and alliances. Specifically in relation to RM, we need to examine what role they will have in creating demand. Will they help in getting patients to participate in clinical trials? What is their role in providing information, including information about alternative treatments, to the public and to primary health-care providers and where they act as clearing houses for services? Are there are any scenarios where they might have conflicts of interests? Are there more effective ways of involving them in RM research, innovation, and clinical introduction and even perhaps in commercialization of RM?

Conclusion

We have provided here perhaps the first taxonomy for evaluating the ethical, economic, environmental, legal and social issues of RM. We need careful evaluation of the advances in RM research as they occur. We need to anticipate what might arise and consider the implications of commercialization and clinical introduction, while taking into account and balancing stakeholder interests. To ensure ethical unfolding, the public should be informed of developments and should be engaged in decision-making. To do this well we must address the issues early, seriously, in a scholarly manner, and in a way that encompasses not only fundamental moral philosophical reflection but also the application of empirical social sciences methodologies.

This combined approach will likely result in practical guidelines and regulations that will on the one hand enable regenerative medicine to develop without unnecessary hindrances, and on the other ensure that any risks are identified early, are addressed adequately and that both patients undergoing research and the general public are protected.

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Notes

1. Morphogenesis and Regenerative Medicine Institute, University of Virginia. http://www.morphogenesis.virginia.edu/index.htm
2. McGowan Institute for Regenerative Medicine, University of Pittsburgh. http://www.mirm.pitt.edu/aboutus.htm#mission
3. http://www.liebertpub.com/ebi/default1.asp
4. http://www.hgsi.com/
5. See www.xtramsn.co.nz/health/0,,8071-2633871,00.html
6. http://www.hfea.gov.uk

References

Atkins, R. and Sefton, M. V. 2001. Tissue engineering the human heart. *New Surgery.* Vol. 1, pp. 26-32.

Benatar, S. R., Daar, A. S. and Singer, P. A. 2003. Global health ethics: The rationale for mutual caring. *International Affairs*, Vol. 79, No. 1, pp. 107-138.

Caulfield, T. A. In Ethical, Legal and Social Issues in Organ Transplantation. Eds. Daar AS, Guttman T and Land W. Pabst Publishers. Munich. In Press.

Caulfield, T. A., Knoppers, B. M., Gold, E. R., Sheremata, L. E., Bridge, P. J. 2003. Genetic technologies, health care policy and the patent bargain. *Clinical Genetics*, Vol. 63, pp. 15-18.

Caulfield, T. A., Sheremata, L. and Daar, A. S. 2003. Somatic cell nuclear transfer: How science outpaces the law. *Nature Biotechnology*, Vol. 21, No. 9pp. 969-970.

Daar, A. S. and Chapman, L. E. 2004. Xenotransplantation. *Encyclopedia of Bioethics*. 3rd Edn. S. G. Post (ed.).

Daar, A. S. and Sheremata, L. 2002. The science of stem cells: Some implications for law and policy. *Health Law Review*. Vol. 11, No. 1, pp. 5-13.

Dossetor, J. B. and Daar, A. S. 2001. Ethics of transplantation: Allotransplantation and xenotransplantation. *Kidney Transplantation: Principles and practice*, 5th edn. P. J. Morris (ed.). Philadelphia, Penn., W. B. Saunders, pp. 732-44. ISBN 0-7216-8297-8299.

The Economist. 2002. The future of mind control. 'People already worry about genetics. They should worry about brain science too'. 23 May.

Fink, J. S., Schumacher, J. M., Ellias, S. L., Palmer, E. P., Saint-Hilaire, M., Shannon, K., Penn, R., Starr, P., Van-Horne, C., Kott, H. S., Dempsey, P. K., Fischman, A. J., Raineri, R., Manhart, C., Dinsmore, J., Isacson, O. 2000. Porcine xenografts in Parkinson's disease and Huntington's disease patients: Preliminary results. *Cell Transplant*, Vol. 9, No. 2, pp. 273-278.

Gold, E. R., Castle, D., Cloutier, L. M., Daar, A. S. and Smith, P. J. 2002. Needed: Models of biotechnology intellectual property. *Trends in Biotechnology*, Vol. 20, No. 8, pp. 327-332.

Haseltine, W. A. 2001. The Emergence of Regenerative Medicine: A new field and a new society. *e-biomed: The Journal of Regenerative Medicine*, Vol. 2, No. 4.

Lysaght, M. J. and Reyes, J. 2001. The Growth of Tissue Engineering. *Tissue Engineering*, Vol. 7, No. 5, pp. 485-493.

Marshall, P. A. and Daar, A. S. 1998. Cultural and psychological dimensions of human organ transplantation. *Annals of Transplantation*, Vol. 3, No. 2, pp. 7-11.

Martin, D. K. and Singer, P. A. 2003. Canada. *Reasonable rationing: International experience of priority setting in health care*. Ham C, Roberts G (eds). Maidenhead, UK, Open University Press, pp. 42-63.

McKneally, M. F. and Daar, A. S. 2003. Introducing new technologies: Protecting subjects of surgical innovation and research. *World Journal of Surgery*, Vol. 27, pp. 930-934.

Mnyusiwalla, A., Daar, A. S. and Singer, P. A. 2003. 'Mind the gap': Science and ethics in nanotechnology. *Nanotechnology*, Vol. 14, No. 3, R9-R13.

Moore, F. N. 2002. Implications of nanotechnology applications: Using genetics as a lesson. *Health Law Review*, Vol. 10, p. 9.

Sefton, M. V. 2002. Functional considerations in tissue in tissue engineering whole organs. *Annals of the New York Academy of Sciences*, Vol. 961, pp. 198-200.

Shamblott, M. J., Axelman, J., Littlefield, J. W. et al. 1998. *Proceedings of the National Academy of Sciences USA*, Vol. 98, pp. 113-118.

Singer, P. A. and Daar, A. S. 2001. Harnessing genomics and biotechnology to improve global health equity. *Science*, Vol. 294, pp. 87-89.

Chapter 7

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*Top Ten Biotechnologies for Improving Health in Developing Countries**

Most research in genomics and related biotechnologies (in the rest of this article, we refer to these simply as 'biotechnologies') focuses on the needs of industrialized nations, a manifestation of the notorious '10/90 gap' whereby 90% of health research dollars are spent on the health problems of 10% of the world's population (Global Forum for Health Research, 2000). Although a few research teams scattered around the world are studying the application of new technologies to health problems of developing countries, their isolated efforts are unlikely to ensure equity of benefit. The World Health Organization (WHO) recently released a report titled 'Genomics and World Health' that highlights the potential of genomics to improve global health. It recognizes that resources devoted to health research in developing countries are limited and that there is an urgent

* Daar, A. S.., Thorsteinsdóttir, H., Martin, D. K., Smith, A. C., Nast, S. and Singer, P. A. 2002. Top Ten Biotechnologies for Improving Health in Developing Countries. *Nature Genetics*, Vol. 32, No. 2, pp. 229-232.

need to focus attention on the most promising technologies. The report recommended that WHO 'should develop the capacity to evaluate advances in genomics, to anticipate their potential for research and clinical application ... and to assess their effectiveness and cost in comparison to current practice' (World Health Organization, 2002). An essential first step in addressing this recommendation is a technology foresight exercise to identify priority technologies. We have now completed a foresight study that identifies the ten most promising biotechnologies for improving health in developing countries in the next five to ten years. It is the first study to provide such information.

How the study was performed

We recruited a panel of 28 scientific experts from around the world (see Web Table A online[1]) who are at the forefront of their fields; about half of them work in developing countries, and the remainder are either originally from developing countries or are well acquainted with public health problems of developing countries. We chose to consult scientists rather than policy-makers or other stakeholders because they are most familiar with current scientific research – a prerequisite for making the sort of judgements that this study requires. A conscious effort was made to balance the proportion of men and women and to represent scientists from various specialty areas and from a range of countries.

We began the study with an open-ended question: 'What do you think are the major biotechnologies that can help improve health in developing countries in the next five to ten years?' Then, as the panelists responded, we asked them to identify the criteria driving their choices. Their responses indicated that the panelists took the following factors into consideration when assessing the importance of the technologies.

- Impact. How much difference will the technology make in improving health?
- Appropriateness. Will it be affordable, robust and adjustable to health care settings in developing countries, and will it be socially, culturally and politically acceptable?
- Burden. Will it address the most pressing health needs?
- Feasibility. Can it realistically be developed and deployed in a time frame of 5–10 years?
- Knowledge gap. Does the technology advance health by creating new knowledge?
- Indirect benefits. Does it address issues such as environmental improvement and income generation that have indirect, positive effects on health?

We used the Delphi Method to achieve consensus (Adler and Ziglio, 1996) (see Web Note A online[2]). We worked with the panelists through several rounds by using combinations of personal interviews, e-mail messages, faxes and phone calls, and analyzed their input to produce the resulting priority list.

The top ten

The results of the study are shown in Table 1. There was a high degree of consensus regarding the top three technologies: all but one panelist included at least one of these among their top three choices. Here we discuss the top three; all ten technologies are discussed in detail in a separate report (Daar et al., 2002).

Table 1 *The top ten biotechnologies with scores based on rankings of the expert panel*

Final ranking	Biotechnology	Final score
1	Modified molecular technologies for affordable, simple diagnosis of infectious diseases	288
2	Recombinant technologies to develop vaccines against infectious diseases	262
3	Technologies for more efficient drug and vaccine delivery systems	245
4	Technologies for environmental improvement (sanitation, clean water, bioremediation)	193
5	Sequencing pathogen genomes to understand their biology and to identify new antimicrobials	180
6	Female-controlled protection against sexually transmitted diseases, both with and without contraceptive effect	171
7	Bioinformatics to identify drug targets and to examine pathogen-host interactions	168
8	Genetically modified crops with increased nutrients to counter specific deficiencies	159
9	Recombinant technology to make therapeutic products (for example, insulin, interferons) more affordable	155
10	Combinatorial chemistry for drug discovery	129

The most highly rated category is 'Modified molecular technologies for affordable, simple diagnosis of infectious diseases'. Early, accurate diagnosis of infectious disease is important not only for prompt treatment, but also to limit the spread of disease and avoid the waste of resources on ineffective treatments. According to panelists, many diagnostic techniques currently in use in developing countries are cumbersome and unsuitable for use in low-resource settings. Molecular diagnostic technologies that are either already in use or are being tested in low-income regions include the polymerase chain reaction (PCR) (Harris, 1998), monoclonal antibodies (Palmer et al., 1998) and recombinant antigens (Aidoo et al., 2001). Modifications can make these technologies more suitable for the developing world; for example, a PCR-based HIV test

that detects the presence of pro-viral DNA in infants has been simplified to use filter paper to process and store blood samples. The DNA can be amplified while the sample is bound to the filter paper, and samples stored this way are heat-stable and can be used for many months (Panteleeff et al., 1999; Beck et al., 2001). Simple hand-held test devices that rely on the binding specificity of monoclonal antibodies or recombinant antigens to diagnose infection may be easily adaptable to settings without running water, refrigeration or electricity (Palmer et al., 1998; Aidoo et al., 2001).

The second most highly rated category is 'Recombinant technologies to develop vaccines against infectious diseases'. Vaccines are a critical component of disease management in developing countries. Recombinant technologies are now at the forefront of efforts to produce new vaccines. For example, as part of the Malaria Vaccine Initiative[3], researchers have tested a subunit vaccine against malaria known as RTS,S/AS02. The phase 1 trial results were promising in adults in The Gambia (Bojang et al., 2001), and phase 2 trials are now underway in children in The Gambia and Mozambique (Lee et al., 2002). Other examples mentioned by panelists include recombinant hepatitis B vaccine (Abraham et al., 1999) and prime-boost vaccine strategies (Belshe et al., 2001). Some recombinant vaccines are already being manufactured in developing countries, sometimes at a fraction of the cost of the standard imported alternative (Abraham et al., 1999).

The third most highly rated category is 'Technologies for more efficient drug and vaccine delivery systems'. Most vaccines and many drugs are administered by injection, and yet tens of thousands of new cases of blood-borne diseases, such as HIV/AIDS and hepatitis B, are caused each year by unsanitary injections (Kane et al., 1999). The enormous expense of refrigeration (maintaining the required temperature can add up to 80% of the cost of vaccine delivery in developing countries) and the inconvenience of frequent dosing are two other drawbacks to current methods of vaccine and drug delivery (World Health Organization, 2001). Alternatives to injections, frequent

dosing and refrigeration could increase safe access to drugs and vaccines, saving millions of lives (Jha et al., 2002). Current alternatives include powdered vaccines, edible vaccines (Langridge, 2000) and controlled-release formulations that replace the need for multiple doses (Jodar et al., 2001).

Assumptions about biotechnology and global health

The results of our survey cast doubt on several common assumptions about the applicability of biotechnologies in developing countries. First, the assumption that biotechnology is irrelevant to the health needs of the world's poor is challenged by the panel's identification of tools that could help control illness in the developing world. Infectious disease can be controlled by molecular diagnostics (rated first) and recombinant vaccines (second). Recombinant therapeutic proteins (ninth) are also relevant to developing countries, where an epidemiological transition is in progress. Today, 60% of all deaths in developing countries are due to non-communicable diseases, and this figure is expected to reach 73% by 2020 (World Health Organization, 1996). Malnutrition could be ameliorated using enriched genetically modified crops (eighth). Panelists also recognized the link between the empowerment of women and health, citing female-controlled protection against sexually transmitted disease (sixth), which can be addressed in part by genomics-based technologies (Boyd et al., 1997; Kelley et al., 2002), as having potential to improve health in developing countries.

Second, our results discredit the assumption that biotechnology cannot contribute to the prevention of disease and the promotion of health. Vaccination is perhaps the best available form of prevention against infectious disease, and the new field of recombinant vaccines (rated second) is already making inroads where traditional vaccines have not been successful (for example, against malaria [Bojang et al., 2001]).

Alternatives to injections and vaccine refrigeration, covered under new systems of drug and vaccine delivery (third), can circumvent the need for refrigeration and reduce the number of new cases of blood-borne diseases caused each year by contaminated syringes. Technologies for environmental improvement (fourth), such as bioremediation, can help transform or sequester unhealthy pollutants in the soil or drinking water, improving public health.

Third, the results of this study suggest that biotechnology, especially molecular diagnositics (rated first), can be made affordable for the developing world. Bioremediation (fourth) is usually less expensive than traditional methods of waste treatment or disposal (United States Environmental Protection Agency), and bioinformatics (seventh), the computer-based analysis of biological data (particularly gene sequences), is surprisingly affordable owing to free data, software and training available online (Butler, 2001; Benson et al., 2001). Enforcement of intellectual property rights will be crucial to the affordability of these technologies. Intellectual property is a complex subject plagued by confusion (Gold et al., 2002). It is encouraging to note that, when the interests of developing countries are concerned, key stakeholders can be magnanimous (Normile, 2000). The University of Ottawa and the University of Havana have decided to forgo the royalties of a jointly developed pneumonia-meningitis vaccine in instances where it is used for strictly humanitarian purposes (R. Roy, personal communication). These sorts of arrangements are breaking new ground in intellectual property rights.

Though we emphasize here the usefulness of foresight and prioritization of promising biotechnologies, we do not wish to suggest that our top ten list comprises the only biotechnologies that have value for improving health in developing countries. Several technologies that scored high in the study but were not among the top ten include proteomics to target proteins and peptides that could be used in vaccines and therapeutic agents; DNA sequence analysis to discover population polymorphisms

that may cause a predisposition to regionally specific diseases; gene-based drug screening technologies for local or traditional medicines aimed at providing affordable medicines while making the best use of local and natural resources such as indigenous plants and snake or insect venoms; and genetic modification of plants for production of common drugs (that is, using plants as bioreactors for drug production).

An appropriate balance

The intention of this study is to highlight the potential of biotechnologies for improving health in developing countries. This focus, however, should in no way diminish the importance of proven health strategies. Health education, for instance, is integral to the control of the AIDS pandemic, as is the provision and use of male condoms. Improvements in sanitation can markedly reduce the incidence of water-borne diseases, and basic nutritional education can help prevent nutrient deficiencies. These tools are available now, whereas the biotechnologies in our top ten list are at varying stages of development. Still, there is increasing evidence of the potential of these biotechnologies for improving the health of people in developing countries. A recombinant vaccine against HIV has successfully completed phase 2 clinical trials (Belshe et al., 2001). If this vaccine proves to be effective, affordable and culturally acceptable, it could be more successful at halting the spread of HIV than many current methods. Thanks to the sequencing of the genome of the malaria parasite Plasmodium falciparum, the drug fosmidomycin has moved in less than two years into clinical trials for the treatment of malaria. Fosmidomycin had already been approved for treating urinary infections; a systematic search of the parasite's genome revealed that it contains an enzyme known to be blocked by this drug (Jomaa et al., 1999; Wiesner et al., 2002).

We ought, therefore, to strive to achieve an appropriate balance between such technologies and conventional strategies. This is not an easy task,

but to ignore the potential of biotechnology is not the answer – not when there is strong evidence of its usefulness. Part of this balance will involve the appreciation that these technologies can be used to improve conventional public health strategies such as vaccines and sanitation.

What next?

This foresight study is a first step towards greater health equity through the application of biotechnology. A number of secondary steps flow immediately from these results. First, we encourage individual countries to assess the appropriateness of these technologies given their national contexts, and to focus on those technologies deemed to offer the greatest benefit. The process and criteria identified in this study can be used to guide these assessments.

We also encourage regional associations of developing countries to examine how they collectively can improve health in their regions by promoting the technologies suggested by our report. Our full report has been accepted for formal consideration by the Science and Technology Commission of the New Partnership for Africa's Development[4] (NEPAD; J. Mugabe, personal communication). NEPAD represents a pledge among African leaders committed to the eradication of poverty and to development of their region. It recognizes the importance of science and technology for sustainable development in Africa.

We urge pharmaceutical and biotechnology industry associations to work with their member companies to determine where the top ten biotechnologies sit in their product pipelines, to explore any impediments to their development, and to work with WHO and developing countries to address access issues for those technologies deemed suitable for diffusion. Such partnerships have been identified as a key strategy in the seminal report titled 'Making New Technologies

Work for Human Development' from the United Nations Development Programme (2001).

Our results can also be used to guide the policy formulation of major international donors and bilateral aid agencies such as the U. S. National Institutes of Health, Rockefeller Foundation, Wellcome Trust, Gates Foundation and the proposed Global Health Research Fund (World Health Organization, 2001).

By providing concrete examples, this study focuses public attention on the benefits of genomics and other biotechnologies for developing countries and thereby sets the stage for more effective advocacy by WHO and others regarding harnessing biotechnology for developing world health.

The top ten list also focuses attention on those technologies that require further assessment. We encourage WHO to conduct a formal technology assessment of key examples from the top ten list of biotechnology platforms to determine their cost effectiveness. Moreover, we recommend that WHO repeat this global foresight exercise on a periodic basis (for example, every two to three years) to keep attention focused on the most promising technologies as the science develops. The process and criteria we have developed in this study would be useful for that purpose.

Foresight exercises such as ours have been found to increase communication, encourage the community to concentrate on the longer term, help foster better coordination among different stakeholders and develop a consensus on a shared future vision and commitment to specific goals (Martin, 1995).

By focusing attention on the most promising biotechnologies, we have taken an important step beyond the WHO report, 'Genomics and World Health', and down the path towards implementation.

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Supplementary information is available on the Nature Genetics website.

Notes

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1. http://www.nature.com/ng/journal/v32/n2/extref/ng1002-229-S2.pdf
2. http://www.nature.com/ng/journal/v32/n2/extref/ng1002-229-S1.pdf
3. Information on the Malaria Vaccine Initiative is available online at http://www.malariavaccine.org
4. The official website of NEPAD is located at http://www.nepad.com.

References

Abraham, P. et al. 1999. Evaluation of a new recombinant DNA hepatitis B vaccine (Shanvac-B). *Vaccine*, Vol. 17, pp. 1125-1129.

Adler, M. and Ziglio, E. 1996. *Gazing into the oracle: The Delphi Method and its implications for social policy and public health*. Jessica Kingsley Publishers, London.

Aidoo, S. et al. Suitability of a rapid immunochromatographic test for detection of antibodies to human immunodeficiency virus in Ghana, West Africa. 2001. *J. Clin. Microbiol.*, Vol. 39, pp. 2572–2575.

Beck, A. I. et al. 2001. Simple, sensitive, and specific detection of human immunodeficiency virus type 1 subtype B DNA in dried blood samples for diagnosis in infants in the field. *J. Clin. Microbiol.*, Vol. 39, pp. 29-33.

Belshe, R. B. et al. Safety and immunogenicity of a canarypox-vectored human immunodeficiency virus Type 1 vaccine with or without gp120: A phase 2 study in higher- and lower-risk volunteers. *J. Infect. Dis.*, Vol. 183, pp. 1343-1352.

Benson, D. A. et al. 2001. GenBank. *Nucleic Acids Res.*, Vol. 28, pp. 15-18.

Bojang, K. A. et al. 2001. Efficacy of RTS,S/AS02 malaria vaccine against Plasmodium falciparum infection in semi-immune adult men in The Gambia: A randomized trial. *Lancet*, Vol. 358, pp. 1927-1934.

Boyd, M. R. et al. 1997. Discovery of cyanovirin-N, a novel human immunodeficiency virus-inactivating protein that binds viral surface envelope glycoprotein gp120: Potential applications to microbicide development. *Antimicrob. Agents Chemother.*, Vol. 41, pp. 1521-1530.

Butler, D. 2001. Bioinformatics to be nurtured online. *Nature*, Vol. 411, p. 513.

Daar, A. S., Martin, D. K., Nast, S., Smith, A. C., Singer, P. A. and Thorsteinsdóttir, H. 2002. *Top 10 Biotechnologies for Improving Health in Developing Countries*. Toronto, Canada, University of Toronto Joint Centre for Bioethics.

Global Forum for Health Research. 2000. *The 10/90 Report on Health Research 2000.* Geneva, Switzerland, Global Forum for Health Research.

Gold, R. E., Castle, D., Cloutier, L. M., Daar, A. S. and Smith, P. J. 2002. Needed: Models of biotechnology intellectual property. Trends Biotech., Vol. 20, pp. 327-329.

Harris, E. *A low cost approach to PCR: Appropriate transfer of biomolecular techniques*. New York, Oxford Univ. Press.

Jha, P. et al. 2002. Improving the health of the global poor. *Science*, Vol. 295, pp. 2036-2039.

Jodar, L. et al. Ensuring vaccine safety in immunization programmes – a WHO perspective. *Vaccine*, Vol. 19, pp. 1594-1605.

Jomaa, H. et al. 1999. Inhibitors of the nonmevalonate pathway of isoprenoid biosynthesis as antimalarial drugs. *Science*, Vol. 285, pp. 1573-1576.

Kane, A., Lloyd, J., Zaffran, M., Simonsen, L. and Kane, M. 1999. Transmission of hepatitis B, hepatitis C and human immunodeficiency viruses through unsafe injections in the developing world: Model-based regional estimates. *Bulletin of the World Health Organization*. Vol. 77, pp. 801-807.

Kelley, B. S., Chang, L. C. and Bewley, C. A. 2002. Engineering an obligate domain-swapped dimer of cyanovirin-N with enhanced anti-HIV activity. *J. Am. Chem. Soc.*, Vol. 124, pp. 3210-3211.

Langridge, W. H. R. 2000. Edible vaccines. *Sci. Am.*, Vol. 283, pp. 66-71.

Lee, E. A. et al. 2002. Induction of T helper type 1 and 2 responses to 19-kilodalton merozoite surface protein 1 in vaccinated healthy volunteers and adults naturally exposed to malaria. *Infect. Immun.*, Vol. 70, pp. 1417-1421.

Martin, B. R. 1995. Foresight in science and technology. *Technol. Anal. Strateg. Manage.*, Vol. 7, pp. 139-168.

Normile, D. 2000. Monsanto donates its share of Golden Rice. *Science*, Vol. 289, pp. 843-845.

Palmer, C. J. et al. 1998. Evaluation of the OptiMAL test for rapid diagnosis of Plasmodium vivax and Plasmodium falciparum malaria. *J. Clin. Microbiol.*, Vol. 36, pp. 203-206.

Panteleeff, D. D. et al. 1999. Rapid method for screening dried blood samples on filter paper for human immunodeficiency virus type 1 DNA. *J. Clin Microbiol.*, Vol. 37, pp. 350-353.

United Nations Development Programme. 2001. Human Development Report 2001: Making new technologies work for human development. New York, Oxford University Press.

United States Environmental Protection Agency. 2001. *Citizen's Guide to Bioremediation*. Washington, D.C., U.S. Environmental Protection Agency.

Wiesner, J. et al. 2002. Structure-activity relationships of novel anti-malarial agents. Part 3: N-(4-Acylamino-3-benzoylphenyl)-4-propoxycinnamic acid amides. *Bioorg. Med. Chem. Lett.*, Vol. 25, pp. 543-545.

World Health Organization (WHO). 1996. *Fact Sheet 106: Noncommunicable diseases: WHO experts warn against inadequate prevention, particularly in developing countries*. Geneva, Switzerland, World Health Organization. http://www.who.int/inf-fs/en/fact106.html.

_____. 2001. *Fact Sheet 169: Global alliance for vaccines and immunization.* Geneva, Switzerland, World Health Organization. http://www.who.int/vaccines/gavi/FactSheet-en.doc (Accessed 10 February 2006.)

_____. 2001. *Macroeconomics and health: Investing in health for economic development (Report of the Commission on Macroeconomics and Health).* Geneva, Switzerland, World Health Organization.

_____. 2002. *Genomics and World Health: Report of the Advisory Committee on Health Research.* Geneva, Switzerland.

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