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Stem cell research

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Managing risk

Myron Scholes: Benefits and chaos from salient events

David Allen: Risk inseperable from business

Sir Ian Prosser: Risk in the boardroom

Zuckerman lecture

Edelgard Buhlmahn: Europe as a global player

THE FOUNDATION FOR SCIENCE AND TECHNOLOGY

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Contrasts in UK, US stem-cell rules

In this issue we present a summary of the Foundation's dinner/discussion on the question "Stem cell therapy — promise or threat?" (pages 3–8). In the months that have passsed since the meeting, most interest has centred on the decision by President George W. Bush on 9 August 2001 that US federal funds could be used to support such research only if the stem cells used derived from one of 60 cell lines established before 9 August, not exclusively in the United States.

The decision and the regulations that have flowed from it do not inhibit privately funded institutions — biotechnology companies and private clinics, for example — from carrying out whatever research they think fit. There is nevertheless legislation by state governments which in some (but not all) states prohibits research with stem cells. The decision is nevertheless seen by the biomedical research community in the United States as a viable compromise between the Bush White House and the Pro-Life lobby, which abhors the use of human embryos (from which stem cells may be derived) for any purpose other than in the treatment of infertility.

The President's decision requires that embryonic stem cells (ESs) eligible for federal support, mostly through the National Institutes of Health (NIH), should have been derived from embryos unwanted in fertility treatments (such as IVF) and that written consent should have been obtained before the founding of ES cell lines. Implicitly, the retrospective character of the decision concedes that federal funds should not be used to support the further use of human embryos for the formation of ES lines.

The NIH duly published (in August last year) a catalogue of the 60 eligible cell lines, 45 of which have been established outside the United States. Sweden (the Karolinska Institute and the University of Gothenburg) offers 25 ES cell lines, India 7, South Korea 3, Australia 6 and Israel 4. It will be for researchers individually to reach agreements with the providers of stem cells on the exploitation of the intellectual property they embody.

The UK position

This contrasts with the legislative position in Britain, where it has been agreed that stem cells may be derived from human embryos created only for that purpose provided that the requirements of the Human Fertilization and Embryology Authority (HFEA) are met. These entail the specific advance licensing of all investigations and that no research with human embryos should continue fourteen days or more after fertilization. In contrast with the United States, the British law applies to commercial and private laboratories. Non-compliance may be a criminal offence.

The basic legislation is the Human Fertilization and Embryology Act of 1990, which also established the eponymous authority, under which the purposes of research with embryos were originally limited to the improvement of IVF (including genetic diagnosis). In 1998 both the HFEA and the Human Genetics Advisory Commission recommended that the purposes of embryo research should be broadened; Professor Donaldson's committee (see page 7) was set up to recommend whether and how that should be done.

The outcome was the HFE (Research Purposes) Regulations 2001, passed by both houses of Parliament in January 2001, which added to the original purposes of research the understanding of the development of embryos and of "serious" diseases and the application of that knowledge to the treatment of "serious" diseases. The regulations were amended during the debate in the House of Lords by the requirement that there should be a formal review of the regulations by a select committee, which has now reported (see below).

In the meantime, the assumption that the HFEA was competent to regulate research directed at the cloning of human beings by the technique of Cell Nuclear Replacement (CNR, used to produce the sheep "Dolly") was challenged by the Pro-Life Alliance, which applied to the High Court for judicial review. The court agreed with the applicants that the 1990 act did not cover CNR in November 2001, whereupon the Government introduced and secured the enactment of a Bill to clarify that the HFEA has authority over CNR experiments. (Subsequently, the Court of Appeal overturned the judgement of the judicial review.)

The select committee's report, published on 13 February 2001, commends the broadened regulations, but recommends that, where possible, human embryos surplus to the requirements of IVF procedures should be used in preference to specially created embryos and that the 14-day limit should remain. It endorses government's proposal that the Medical Research Council should establish a stem-cell bank and that there should also be regular reviews (by HFEA) of the outcomes of licensed research.

On two matters, the select committee asks for clarification of the regulations as they stand: the meaning of "serious" in the phrase "serious diseases" and the meaning of "informed consent" in the light of the possibility that stem-cell lines may be maintained indefinitely, or be "immortal". Consonant with British practice, the committee sets its face against financial rewards for the donation of embryos.

In reference to claims that stem cells may be derived from tissue-specific stem cells derived from adult human beings, thereby avoiding the use of embryos as a source, the committee suggests a further review "perhaps towards the end of the decade" to decide whether research with "human embryos is still necessary". This possible route to pluripotent stem cells has been suggested by reports that tissue-specific stem cells can be induced to de-differentiate (or to lose their specificity for particular tissues) and is widely canvassed by pro-life groups as an alternative route to stem-cell therapy. Two research reports recently published in *Nature* suggest that earlier researchers may have been misled by the spontaneous fusion of stem cells with tissue cells. ❐

Useful links

http://www.parliament.the-stationery-office.co.uk/pa/ld200102/ldselect/ldstem/83/8301.htm
A 'browsable' version of the Report from the Select Committee, Stem Cell Research (HL 83(i) ISBN 0 10 442052 9), published in February 2001.

http://www.nih.gov/news/stemcell/
A recent addition (28 February) to the US National Institutes of Health's site outlines their strategies for implementing human embryonic stem cell research.

http://www.stemcellresearch.org/news.htm
An impressive array of links to the latest in stem cell research. Produced by The Coalition of Americans for Research Ethics, whose aim is to "promote scientific research and health care which does no harm to human life", their dedication ensures that the site is up-to-date and covers the ground.

The science of stem-cell research

Professor John Clark OBE FRSE

Stem-cell therapy: promise or threat

The rapid advance of embryo research and reproductive medicine make this an area of vital public interest. At a joint meeting of the Foundation for Science and Technology and the Academy of Medical Sciences, on 31 October 2000, the ethics of stem-cell, research were discussed. The speakers presented the ethical dilemma facing society against the scientific facts of the matter. A full summary of the discussion, by Sir Geoffrey Chipperfield, appears on the Foundation's website.

John Clark is Head of Gene Expression and Development, Roslin Institute, Edinburgh.

My brief is to outline the technical background and to give a glimpse of the promise of stem-cell and cloning technology — and the possible dangers. There are two technical approaches at the centre of this new technology, nuclear transfer and the use of pluripotential stem cells.

Nuclear transfer

Nuclear transfer has been around for a number of years but it was the pioneering research of my colleagues at the Roslin Institute, Ian Wilmott and Keith Campbell, that showed that this approach could be applied to mammalian species. The cloning of Dolly the sheep, in 1997, was a milestone in this work.

The procedure starts with an unfertilised egg, the genetic material from the mother. The genetic material is removed from the egg using, in effect, a small glass needle. The cells that are being used to donate genetic material to 'program' that egg are then injected under the basal membrane of the egg. The cytoplasms of the original oocyte and the donor cell fuse, and eventually the nucleus from the donor cell is present within the cytoplasm of oocyte from the donor.

The reconstructed eggs are then transplanted back into a recipient, normal fertile female, and in a relatively small proportion of cases, normal development can take place, resulting in the production of a cloned animal.

When this technology first came into being, the media concentrated on its use to clone animals. But the efficiency of this process remains low. In some laboratories, and in certain species, including cattle, the method is becoming more efficient — up to 15% of reconstructed embryos can develop into a fully normal animal.

In the years since this technology hit the headlines, the importance of what these experiments have told us about the biology and the development of organisms has become apparent.

Before the advent of mammalian cloning from differentiated cells, there was very much a dogmatic view about how mammals developed. The oocyte is fertilised, it then develops to become the early embryo which then differentiates into all the complex tissues that go to make a fully grown animal.

Of course, you could take cells from that animal and grow them in tissue culture. You could even put some of those cells back into that animal — effectively a form of transplantation. But the dogma was that it was a one-way process. It started with the egg, the oocyte, and after fertilisation progresses through the embryo to the adult animal and to those somatic tissues. (Somatic tissues comprise the differentiated final tissues in a body — muscle cells, liver cells, brain cells and the like.)

But the Dolly experiment showed that all was not quite as it seemed. If the nucleus of a somatic cell is put into the oocyte, to produce an embryo, it is possible to complete the developmental circle — virtually to go backwards through development.

Pluripotential stem cells

Pluripotent stem cells, or embryonic stem cells, are cells derived primarily from an early embryo. Pluripotent cells were first isolated in the mouse more than 15 years ago and so we know a lot about the properties of these cells, at least for mouse cells. In humans these cells are isolated from a very early embryo, the blastocyst, five to six days after fertilisation of the oocyte. They can grow in cell culture and have the crucial ability to differentiate into somatic tissues. These cells are pluripotent in terms of having the total potential to make every cell type in the human body.

Pluripotent stem cells can be established in cultures and will grow, in an immortal sense, for many generations. To establish these cell lines, we need to disaggregate these embryos, extract the inner cell mass and convert them into an 'established' cell culture.

These embryos normally consist of 100–120 cells when the experiments to isolate the inner cell masses and establish the embryonic stem cells or pluripotential stem cells are carried out. What are the properties of these stem cells? First, we can grow them for a very long time — for human cells, we can culture them for more than two years. Cells derived from mice have been cultured for many years. As these cells are virtually immortal, we don't lose them. This contrasts to stem cells taken from an adult, which are very difficult to grow for long periods.

How can we use these human pluripotential cells? Although the answer to this

question is generally transplantation technology, it is worth remembering that there are other applications. For example, if we can make pure populations of human nerve cells or human liver cells, we can use those cells for testing the toxicological properties of drugs. And with the human genome sequence virtually cracked, in the 'post-genomic' era a tractable source of human cells is the ideal place to discover how these genes are expressed in specialised cell types.

An *in vitro* source of normal human cells also gives us the possibility of performing cell transplantation — or regenerative medicine. Parkinson's disease, spinal-cord injuries, strokes and diabetes might be treated in this way. And human pluripotent cells might be a source of heart-muscle cells for use in treating congestive heart failure.

This technology is still in its infancy. We have a lot to learn about just how to grow populations of human pluripotential stem cells. We have to learn how to scale-up the process if we are ever going to use these cells as a genuine medical resource.

We need of course to be able to control these pathways. Yes, they can form a nerve cell, liver cell or, potentially, a pancreatic cell. But we don't really yet know the molecular biology behind the signals that control that pathway. We will need to understand these steps in developmental biology before we can prepare, say, a pure population of neurons for treating Parkinson's disease.

There are also safety issues. We grow these cells in the test tube in the laboratory. If we are going to use them as a therapeutic intervention, they will be subject to the same stringent regulatory requirements that normal drugs have to meet. We don't yet know how safe it will be to put these types of cells, or cells derived from them, back into humans.

Finally, there is the issue of immune rejection. The only really safe type of transplantation, immunologically speaking, is from self to self. If we are making embryonic stem cells, then as we try and make those for transplantation, they will potentially be seen as foreign tissue by the individual to whom we are trying to make the transplant and will be rejected. For the transplants to be successful, those people would have to be kept on quite severe regimes of immunosuppression. The ideal would be to transplant the equivalent cell from 'yourself' back into 'yourself', known as an autologous transplant.

Therapeutic cloning

Therapeutic cloning is the link between the two themes of this article. It involves taking a somatic cell from a patient, a skin cell for example, and transferring the nucleus into an oocyte, as described above. An early embryo developed from that oocyte is then used as a source of pluripotential cells. If the therapy requires neurons, the conditions encouraging pluripotent cells to differentiate into nerve cells would be used, and the resulting neurons transplanted back into the patient. Cells produced in this way would be an autologous transplant, self-to-self.

In principle that sounds quite simple, but it is a complex process in practice and is by no means a routine procedure. And of course there are important ethical considerations.

We know that the oocyte is — at present — the only cell capable of fully reprogramming a differentiated adult cell. But, of course, we are never going to be able to get a supply of oocytes sufficient for this to become a routine part of medicine. Rather, we need to understand what the oocyte is actually doing when it reprograms a somatic cell through the early embryo and ultimately to become a pluripotential stem cell.

Most of this work is being done in animal models, mainly sheep and mice, but if this kind of technology is to become a reality for medical treatment in humans, it will be necessary for some of these experiments to be performed in humans. We will have to understand how the human oocyte does this reprogramming. The majority view of the scientific community is that there is a need that this 'human factor' should be understood, with the aim of combining stem-cell and nuclear-replacement technologies for medical purposes. ❐

discussion

A recurring theme in the discussion was a deep concern about the gap between public understanding of the issues and the scientific and ethical principles underpinning the research. Examples cited included the semantic debate about the use of the word 'embryo'. An oocyte that has had a somatic nucleus transferred to it and is not implanted is not an embryo, nor is it a human being: it is material with the potential to become a human being in quite different circumstances. It is the equivalent to vegetative reproduction in plants. Why, then, use the word 'embryo'? Because not to use the word would raise the charge of being devious, and the widespread distrust of scientists would lead people to assume they were being tricked.

There is a widespread view that research on stem cells differs in some major way from all previous research, because scientists cannot predict with certainty its benefits, and because it might be misused. The view in the scientific community, though, is that this research is no different from what has gone before. Nevertheless, the fact is that public hostility will persist, and inform political activity until there is clear evidence of the beneficial therapeutic results of the research. There was debate about when this was likely to be — some thought 30 years, others 10. It was suggested, however the research should not be justified solely on the basis of future benefits. The true justification lay in the search for knowledge.

Some participants raised fears that, while research in this country could be adequately controlled, the same might not be said of some other countries. The UNESCO prohibition must be monitored and enforced. But scientific research takes place in an intensely competitive world, and if we do not use our research capability here, others — particularly in the United States — will take the lead. It is important for UK legislation to keep up with advancing science. Ten years ago the Human Fertilization and Embryology Act had permitted research on embryos for certain purposes. Now, new research has shown that for other therapeutic purposes, research should be permitted. The scientific community should continue to press for new legislation to recognise this.

⇨ ***A detailed summary of the discussion is available on www.foundation.org.uk***

Stem-cell research — why is it regarded as a threat?

Professor Peter Lachmann FRS FMedSci

Peter Lachmann is President of the Academy of Medical Sciences, and Emeritus Professor and Fellow of Christ's College, Cambridge.

I take it as established that stem-cell technology has great promise for the treatment of a variety of diseases and, indeed, that cell therapy may be among the most exciting prospects for medical advance in the first decades of the new century. So why has the prospect of stem-cell therapy been greeted not as an innovation to be welcomed but as a threat to be resisted?

In part, this is a Luddite reaction from those who regard all innovation as threatening and who look back nostalgically to a (fictitious) golden pre-industrial past. There are, however, also several counter-arguments that that deserve to be taken seriously: I shall deal with five of them.

Argument 1

That stem-cell technologies would be very expensive and available only to rich countries and to rich people.

True, nearly all novel medical technologies are expensive, but they soon become cheaper as the scale on which they are used increases. A good example is bone marrow transplantation, which initially required a dedicated team to treat a single patient. Just a decade or two later, bone-marrow transplantation has become routine in leukaemia cases. The same will almost certainly be true of therapeutic agents, be it β-interferon for multiple sclerosis or monoclonal antibodies for the treatment of cancer.

Furthermore, in the United Kingdom the National Health Service makes all treatments generally available if they have been approved as of clinical value by the National Institute for Clinical Excellence.

There is a further argument for not taking this the 'cost' argument too seriously. The major medical advances in the past 50 years have come in the control of disease rather than in its cure. This has led to a great increase in the cost of healthcare as large populations of, particularly, elderly people live a good quality of life which depends on the long-term administration of drugs, for example for the treatment of high blood pressure, diabetes and rheumatoid arthritis. Even for diseases that cannot be adequately controlled, such as Parkinson's disease, continuous therapy over many years is given to alleviate the symptoms.

The great promise of stem-cell therapy is that it may indeed lead to cures for such diseases. If it becomes possible virtually to cure Parkinson's disease or diabetes, the net result would be a reduction in the cost of healthcare in a number of currently incurable but treatable diseases.

Argument 2

That stem-cell research would divert efforts from other health strategies.

This is another argument that does not bear close examination. Nobody can tell in advance what research will yield what benefits. The research from which the current interest in stem cells arose was the fundamental study of developmental biology; its outcome could not have been foreseen. Moreover, current research into the mechanisms of cellular reprogramming and the growth requirements of different cell lineages is likely to prove of widespread value in human biology and medicine. It will also advance scientific knowledge.

The first two arguments are based on economics, the remainder deal with ethics, so should perhaps be given greater weight.

Argument 3.

Interference with the genome involves "playing God".

This view is derived from the idea that the divine creation is perfect and that it is therefore inappropriate to try to alter it in any way. In a country such as England, where every acre of land bears the marks of sustained human activity and where no primordial wilderness remains, this argument seems inappropriate. Ever since *Homo sapiens* took to herding animals and to agriculture, the species has modified the environment. Our major food plants and domestic animals have been extensively modified by human intervention. The idea that the genetic interventions now being proposed for food plants, for animals and for the therapy of human disease are a categorical break from what has gone on throughout human evolution is impossible to sustain.

The proposition that any attempt to

interfere with perfect divine creation is morally wrong is not widely held even by theologians. Thus Professor Ian Torrance, Professor of Divinity at Aberdeen, says that: "Creation, understood in the light of the trajectory of the incarnation… is an enabling act… [one] in which a created realm is brought to its own reality and enabled to be itself. … I believe we have an authority to intervene, so as to heal and restore, but not to manipulate and destroy."

Confusion on this question no doubt arises from the idea of a 'perfect creation' adopted by the early evolutionary biologists, who tended to replace a perfect divine creation with perfect evolutionary adaptation. Yet study of the molecular mechanisms of evolution show a different picture. Evolutionary adaptation is by no means a perfect process but very much a matter of "muddling through".

No competent engineer would design a creature walking on two legs as badly adapted to the upright posture as is Man. The problems mankind has with necks, backs, hips, knees, ankles and feet reflect imperfect adaptation to the upright posture. If we accept that evolution just does the best it can with the molecular mechanisms to hand, we would worry less about the morality of putting fish genes into tomatoes or foreign genes into ourselves.

The idea of "playing God" also carries with it the proposition that there are things it may be too dangerous for mankind to know. This pernicious proposition finds few defenders in democratic societies. On the other hand, there is general agreement that there are things that should not be done — in science as in other areas of life. The intention of stem-cell research is to produce treatments for human diseases. It is difficult to regard that as an unworthy end and even more difficult to see the moral objection to curing the sick.

Argument 4

That somatic-cell nuclear transfer is immoral as it involves creating embryos only to destroy them.

The essential problem here is to decide at what stage of development a human embryo acquires the interests — and the rights to protect these interests — that characterise a human being. The question has occupied a great deal of theological and philosophical attention.

Two conditions are regarded as sufficient to confer interests and rights to defend them: sentience and intentionality, of which sentience is the less controversial and the more fundamental. Sentience in this context is not identical to the ability to think nor is it wholly identified with the ability to feel pain. Sentience must surely be equated with the ability to form links with the outside world. Until an organism has a rudimentary central nervous system and sense receptors of some kind, it cannot form any contact with the outside world and therefore is not sentient.

Intentionality, which derives from more utilitarian considerations, is also clearly impossible until an organism is sentient. It therefore does not seem possible to attribute either sentience or intentionality to a pre-implantation embryo, or indeed even to an implanted embryo until it has developed some form of nervous system and some sense organs. Consistent with that opinion, it is now universally accepted that a human being has died when no contact with the outside world can be demonstrated by central nervous function.

Church doctrine on this question has fluctuated. The mediaeval church took the view that an embryo acquires a soul (*animatus*) when it acquires recognisable human form (*formatus*). The mediaeval church held that the abortion of an embryo that was neither formatus nor animatus was only a fineable offence; only after an embryo had become animatus did an abortion became a mortal sin. This doctrine was changed by Pius IX in 1869 when he declared that an embryo acquired full human status at fertilisation. That decision is likely to have been influenced by a desire to bring Christian doctrine in line with nineteenth-century embryology, but is at the core of the refusal of the Roman Catholic Church to countenance embryo research. The view is not widely shared by other religions.

Nor can it be sustained. Large numbers of pre-implantation embryos are lost throughout the reproductive life of women. These embryos are not mourned, they are not given burial and nobody says prayers for them. The intrauterine coil, widely used as a method of contraception (though not permitted by the Roman Catholic Church) is specifically designed to prevent implantation of embryos and, again, is not widely regarded as morally reprehensible.

Further difficulties for the view that full human status is acquired at fertilisation arise from the advances in reproductive biology that are the basis of stem-cell research. Somatic-cell nuclear transfer involves no fertilisation and so reduces the Pius IX doctrine *ad absurdum*: any somatic cell whose nucleus can be introduced into an oocyte can possibly give rise to a complete human being. That difficulty may become more acute if the reprogramming of cells can be achieved without using an oocyte, for then any somatic cell will have the potential of being grown into a complete embryo and, in principle, into a human being. This would logically mean that one should ascribe a moral status to every cell in one's body — a concept that is clearly ridiculous.

The view that an embryo acquires the status of a human being gradually and not fully until it is obviously of human form, with a central nervous system and organs (the Protestant view) or even until it is delivered (as in the Jewish religion) is philosophically more readily defensible than saying that full human status is acquired at fertilisation. The particular point in development at which an embryo acquires full human status must be to some degree arbitrary. Similar difficulties arise in distinguishing between plants and animals, between male and female and between the living and dead at the end of life. The fact that making distinctions can sometimes be difficult is no argument for making fundamentalist distinctions or for refusing to make a distinction at all.

Argument 5

Allowing stem-cell research is the thin end of a wedge leading to neo-eugenics, 'designer' children and discrimination against the less-than-perfect.

The 'Principle of the Wedge' was enunciated by Francis Cornford in the *Microcosmographica Academica*: "you should not act justly now for fear of raising expectations that you may [be able to] act still more justly in the future — expectations which you are afraid you will not have the courage to satisfy… the argument implies the admission that the persons who use it cannot prove that the action is not just. If they could, that would be the sole and sufficient reason for not doing it."

In the present context, the Donaldson proposals forbid the re-implantation of embryos used for stem-cell research. There are cogent biological reasons for opposing reproductive cloning using cell nuclear transfer. This is a form of vegetative reproduction, a technique used by plants but not, in general, by animals. The late William Hamilton pointed out in 1990 that primitive animals that have the opportunity of adopting vegetative reproduction have uniformly failed to do so and argued that the risks of parasitism make sexual reproduction, with its re-assortment of genes at each generation, advantageous in evolutionary terms.

The use of reproductive cloning can be defended for farm animals, where it is possible to maintain the necessary genetic variability in frozen embryos and where this technique may be the best for producing, for example, a herd of cows resistant to BSE. Such techniques should not be applied to humans and their widespread use might be evolutionarily harmful. We

are also not yet sure that somatic cells used for generating embryos may not have mutations that are potentially harmful in one gene copy of a pair of genes. This is not a problem when using stem cells, nor is it a problem in the first generation of a cloned animal, but it could give rise to problems in later generations.

Furthermore, the UNESCO universal declaration on the human genome — which UNESCO hopes will be incorporated into national laws — specifically prohibits the use of genetic manipulation to produce "enhancement" rather than for the treatment of disease. Although vigilance will certainly always be needed to prevent the misuse of many novel technologies, it is unlikely that the use of stem cells carries any particular dangers of this kind.

I conclude with another quotation from the *Microcosmographica Academica*: "There is only one reason for doing something; the rest are arguments for doing nothing". The Luddites can always produce a variety of more or less plausible arguments for resisting innovation. Without innovation, we would not have passed from the Stone Age to the Silicon Chip age in not much more than 100 generations. The present arguments for doing nothing are no more potent than all their predecessors. ❐

The ethics of stem-cell research

Professor Robin Gill

Robin Gill, Michael Ramsey Professor of Modern Theology, University of Kent at Canterbury.

Let me first give a cautious welcome to the prospect of stem-cell research for therapeutic purposes and to the Donaldson Report. There is the prospect of real benefit for very vulnerable people emerging from this research. Anyone who has pastoral or personal contact with those suffering from, say, Parkinson's or Alzheimer's disease will surely wish to find a cure and will welcome scientists who are attempting to do this. Where people differ is not usually about the ends of this research, but about the means.

Some will be convinced on religious grounds that the early stages of stem-cell research involve the creation and subsequent destruction of embryos, this research is intrinsically wrong. I respect this position but I do not hold it myself. Others will argue on a purely utilitarian basis that the therapeutic advantages of stem-cell research override any scruples about human embryos or fears about human reproductive cloning. Again this is not my position. I argue, more cautiously, that our duties towards the sick and vulnerable (which I take to be at the heart of Jewish and Christian ethics) should be given priority over our duties towards those embryos that should never be implanted. Yet, since we also have a duty to society at large (a duty fundamental to Jewish, Christian and Islamic ethics), we should be properly cautious about research that may pave the way for others to do something that is intrinsically wrong, namely to attempt to clone human beings.

The case against

The Donaldson Report acknowledges that, in the early stages at least of stem-cell research, it will be important to create cloned embryos using cell nuclear replacement (CNR) in order to provide stem cells suitable for therapy. Even if it becomes possible to rely entirely upon adult cells, initial research will involve the creation and then destruction of CNR embryos. For those who believe that any embryo from the time of fertilisation should be accorded the same right to life as a baby or as an adult, this procedure clearly involves the deliberate killing of an innocent human being. It is therefore intrinsically wrong and stem-cell research, if it depends upon this in the initial stages, is itself intrinsically wrong.

The background to this strong religious objection to stem-cell research is summarised in Peter Lachman's article (see opposite). The conservative position is undermined by inherent inconsistencies, but what is the moral alternative?

One could hold that embryos have no moral status and that we have no corresponding moral responsibilities towards them. Some philosophers have argued that it is our ability to think which gives us moral status as human beings. As embryos cannot think, they have no such status. This view is seriously deficient in two crucial respects. First it has very damaging implications for those with severe learning disabilities and for the elderly with reduced intellectual abilities, and second it privileges intellectual capacity. As a theologian I am highly suspicious of those intellectuals who claim that it is intellect alone — rather than, say, a capacity to be loved — that makes us truly human.

The middle way

The Donaldson Report argues for "a middle position", according to which "the special status of an embryo as a potential human being is accepted, but the significance of the respect owed to developing human life is regarded as increasing in proportion to the degree of development of the embryo".

Like a number of other religious ethicists, I share this notion of progressive

moral responsibility. It does seem to match practical experience. Yet it lacks the moral clarity of the conservative position. It offers no clear guidelines about how much respect is required at each stage of development. Nevertheless, it is on this basis that the Donaldson Report concludes that at the very early stages of development "it is morally justified to use embryos for research purposes in order to benefit others, provided that [it is] justified by the benefit it may produce".

There are problems with this argument. Suppose that in the long run there no tangible therapeutic benefits. Presumably then the ethicist must conclude that the research was not after all morally justified. All that you can safely say in the present is that, if all turns out as you hope or expect, then you will be morally justified. But of course if it does not then you will not. Not a very satisfactory moral position. Or is it simply the hope or expectation that matters? As long as you hope or even expect that the research will yield therapeutic benefits, then it is morally justified… you are 'acting in good faith'. Undoubtedly acting in good faith is important for ethics (and indeed for theology), but do good-faith hopes or expectations outweigh the moral respect we should have for human embryos?

Sensitivities

The Donaldson Report recalls that it was precisely the issue of research on embryos that divided the original Warnock Committee almost two decades ago. Nine members argued in favour of such research (albeit with careful conditions) and seven dissented, including the only theologian on the Committee, my late colleague Professor Tony Dyson. The Donaldson Report had no dissenters. So perhaps after a decade of research on embryos (a few of them deliberately created for research purposes) we have begun to lose our moral sensitivities in this area. So, just as we agonised about legalising induced abortion in the 1960s, applying strict criteria at the time, and then largely stopped agonising with the passing of time and some several million legalised abortions later, so now, it might be argued, we have become morally desensitised about creating and destroying human embryos for research.

Perhaps this is too harsh, but caution is needed before we become too enthusiastic about research on human embryos. The Donaldson Report cannot be accused of such a view, but it is possible that a shift in consensus between Warnock and Donaldson might one day be followed by a shift towards the expendable-human-tissue position. The Donaldson Report, when contrasted with the Warnock Report, may provide critics with evidence that this is so.

Reproductive cloning

The other troublesome ethical issue raised by the prospect of stem-cell research also involves a slippery slope, or, as I prefer to call it, procedural and moral deterioration. Creating embryos by cell nuclear replacement is the first step in human reproductive cloning. The Donaldson Report insists that the sort of regulatory powers of the Human Fertility and Embryology Authority are sufficient to ensure that CNR embryos are never developed beyond fourteen days and are never implanted. Or to summarise this in language that the report dislikes, a firm line is drawn between therapeutic and reproductive cloning.

I, too, believe that this firm line should be drawn and so, I suspect, do most people. But the trouble is that even if it is drawn in Britain and the rest of Europe, will it be drawn elsewhere? More than that, the knowledge gained in Britain about human CNR will doubtless be very valuable elsewhere in the world to those determined to embark upon human reproductive cloning. In an age of morally responsible science, it is no longer sufficient to say 'knowledge is knowledge' and wash our hands of any responsibility for how this knowledge might be used by the less scrupulous. I am convinced that attempts to clone human beings are intrinsically wrong since it is always wrong to attempt risky interventions on human beings without their consent and with few if any obvious human benefits. If this is so, then stem cell research using CNR embryos in Britain may pave the way for something intrinsically wrong to happen elsewhere in the world, namely attempting to clone human beings. It is not sufficient morally to say, as the Donaldson Report says, that Britain already has the kind of regulatory powers to stop such procedural or moral deterioration. In a global context Britain clearly cannot have such powers.

So the caution in my welcome for the Donaldson Report is based on two distinct fears. First, that we may be becoming less and less sensitive to the propriety of creating embryos for research, and second that unwittingly we may be taking a step along the path to human reproductive cloning. I am not sure that the report adequately addresses these two fears. Indeed, I am not sure that I can adequately address the second fear myself. All technology is power and, in a global context, it can be used by good and bad people alike. It will surprise few of us to discover that genetic and medical science can similarly be used for beneficent and maleficent ends. Sadly we may yet conclude that this is possibly so for well intended stem-cell research as well.

However on the first fear there is more to be said. There is a crucial difference between embryos cloned by CNR and non-cloned embryos, namely that it would be intrinsically wrong (given my earlier argument) to implant the former but not the latter. From a scientific perspective both could be implanted and might indeed be able to gestate to term. In this respect both differ from a vesicular mole which, although fertilised and alive, could never gestate to term. My distinction here is between could and should. CNR embryos could technically be implanted, but morally (and indeed legally) they should not be. It is not simply that we do not intend to implant such embryos but that it would be intrinsically wrong to do so.

In contrast, there is rarely any moral interdiction against implanting non-cloned embryos. Even in rare cases such as the recent baby Nash, where it was considered preferable to implant one embryo rather than another, it is not morally forbidden for any non-cloned embryo to be implanted (even an embryo with some genetic disability). At most we are talking about moral preferences here. The Nash family wanted to have a baby who could save his sister's life rather than a baby who could not. But with CNR embryos it is intrinsically wrong to implant even though it is technically feasible. This is not a moral preference but a moral interdiction.

If this is so, our duties towards a CNR embryo are distinctly less than towards a non-cloned embryo. From a moral (and perhaps legal) perspective a CNR embryo is never a potential baby, so it would not be appropriate to accord it the sort of respect that we should give to a potential baby. Indeed, given a choice between medical research upon animals that involves them in pain and research upon a CNR embryo, then I would reluctantly choose a CNR embryo. My reluctance here is based less on the status of such an embryo than its link to human reproductive cloning.

I have concentrated on the widespread reluctance to accept stem-cell research. It is always important to guard against maleficence. Yet our duty to help sick and vulnerable people convinces me that this is morally justifiable research. Of course, we need to be vigilant about the path that could lead to human reproductive cloning. Yet we do not have a duty to treat CNR embryos themselves with the same moral respect as non-cloned embryos. Furthermore, our duty towards sick and vulnerable people is overwhelmingly more significant than any minimal duty we may have towards CNR embryos. Using such embryos wisely to develop stem-cell therapy does seem to be morally justified. ❐

Benefits and chaos from salient events

Professor Myron Scholes

Managing uncertainty

The presentations reported here formed the final workshop of a three-week programme at the Isaac Newton Institute for Mathematical Sciences in Cambridge. The aim of the programme was to bring two contrasting perspectives of risk together — that risk is a matter of subjective judgement or simply a numerical calculation. At the final workshop a group of people who serve or had served on company boards, discussed risk analysis and corporate governance.

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I shall begin with order and disorder. Financial and other markets behave as if they are ordered, they seem to evolve. So people conclude that what was observed in the past is predictive of the future. That's true up to a point, but from time to time events occur — salient events, I call them — that change the nature of the underlying process. Salient events are more numerous than we think. Thinking about, and dealing with, such events is central to risk management.

A good example is the volatility of the financial markets in the mid-1970s. There had been nothing like it since the 1930s. Gross returns on investments became virtually zero and soon we saw the evolution of novel technologies, ways of measuring and trying to handle uncertainty. Later, a whole range of novel financial instruments was born — index funds, financial futures, hedging contracts and options. The shock caused by the increase of volatility directed attention to understanding and mitigating volatility. Although new regulations evolved, there was also more deregulation, as a result of which institutions and businesses became more competitive in the marketplace.

There are many other examples of how salient events create first shock and then improvement. The collapse of the Japanese market from the early 1990s has essentially halted growth in Japan. As a result of the collapse of a bubble in asset values the state now owns bankrupt banks and, through them, many bankrupt corporations. Japan has spent ten years looking for a solution, without success. Yet in Japan now, alongside the mortified banks and the bankrupt older companies, you find a whole new growth of new businesses.

The euro is another example. A unified currency requires a set of rules that countries must follow; for example, they must not borrow above a certain percentage of gross domestic product. One consequence is reduced economic growth, even recession. But there have also been dramatic structural changes — mergers and regulatory evolution, for example. Of course, tremendous uncertainty persists about the economic infrastructure, one reason why the euro is weak against the dollar.

Similarly, the Asian financial crisis has now led to new enterprises, new rules, new understanding of how to proceed in the future; there will be less reliance on own governments and large conglomerate organizations and more on entrepreneurship and global markets. The financial crisis following the Russian default in 1998 created a global lack of liquidity, but that spurred the development of new technology for risk and liquidity management.

The market collapse in the United States in 2000 points to other issues. The value of old investments has fallen, there has been a slow-down around the world.

What will happen? It takes time for new investments to be decided. Given the capital shock, corporations cannot move capital instantaneously to new activities. After a shock, time slows down while people work out exactly how to invest and where to grow. That is where we are now. When our understanding of the new investment routes is richer, there will be new growth; new models will apply in the technology sphere. The opportunity set will be potentially richer because of the new learning but the direction in which to go will take time to decide.

Plainly, salient events are not rare. And though we learn from them, it is at a cost. But such events will become more common. Time after time, we shall believe that we understand things and then there will be another shock bringing investment to a stop. We will need new ways of tackling old problems.

In Silicon Valley, they say we need 'mushware', an amalgam of ideas and thinking technology, to solve problems in an increasingly uncertain world and to understand the implications of salient events. For corporations, the question of how to manage creative teams of people demands novel thinking in an ever-more chaotic environment in a global economy. That will be an increasingly important issue in corporate governance.

So will be the issue of uncertainty. We, of course, model uncertainty, even in a complex environment. If there is a high degree of certainty, the lowest-cost solution is often to build hardware, say a factory; it is analogous to a low-cost light-switch that only turns on and off. But as uncertainty increases, flexibility becomes more valuable, and production processes move from hard-wired solutions to more costly but more valuable software and model-based solutions that are more adaptable to unanticipated changes. And if salient events occur, both existing hardware and software may become obsolete and the greatest flexibility may come from buying an option to wait — or, rather, using the time to develop the new models that will emerge from the

chaos. That is where the telecoms and computing industries are now.

I will consider the tools of risk management under three headings: risk shifting, diversification and insurance. Risk shifting is just selling the source of risk. If you don't want a particular risk, you do not invest in it. An alternative is for corporations to keep reserves as a hedge against risk. How much to hold in reserves depends on the cost of holding them and the benefits, not easily calculated due, in part, to tax and asymmetric information concerns.

Diversification confronts a fundamental question for a corporation, the balance between owned physical assets and supplies available on the market. Although a corporation may have expertise in a particular part of the supply or distribution chain, it doesn't have to be in all parts of the production process if it can rely on markets. This is a fundamental issue in risk management.

The third dimension of risk management is insurance, by which corporations can buy protection against various events.

There is also a fourth dimension that I think about from time to time: the consequences of the costs of adjustment to chaotic times. This links risk management with liquidity management. It is easy to invest money in assets, but much more difficult to turn assets back into money. Moreover, the cost of moving from assets to money is not constant over time.

The B2B (business-to-business) world illustrates the difficulties. In recent years, web-sites emerged offering to transfer resources among corporations and potential consumers in novel ways. The problem is that, whatever the excellence of a site's technology, these markets do not provide liquidity. There was nobody willing to make a market, and without people willing to transfer and hold inventory and carry it forward, corporations cannot rely on these services to be there in difficult times. They cannot use its services.

This is now one of the central areas in risk management. The focus of corporate decision-making should be on liquidity, especially when the price of liquidity changes. When everybody wants to move from assets to cash, the price of liquidity soars. It is as if everyone in Cambridge tried to sell their house at the same time and move to Oxford — it would not be possible even if it were desirable.

I'll conclude with a few remarks on risk management by sovereign states. In December 2000 in Chile I gave a talk to economists involved in government, and they asked me fundamental questions. What if a country ends up virtually bankrupt? How do we handle liquidity crises or shocks in which the currency deflates dramatically, liquid capital leaves the country or is idle as in Japan today, and little capital investment comes into the country?.

Notice that all of these questions are reactive, not pro-active. One pro-active response for Chile is to diversify to reduce its risks. But Chile cannot diversify sufficiently at low enough cost to affect its risks significantly. Chile must continue to concentrate on its own current activities so it must move to consider managing risk in alternative ways.

It is curious that Chilean economists spend considerable effort on understanding the implications of their current account budgets, its capital account budgets and other considerations — but there are no risk budgets. In Chile, if they had been thinking about risk management, the question would have been, "How can we be proactive?" There are endless opportunities involving risk transfer and insurance. Chile could hedge risks that create costs. Chile could use the capital markets to transfer risk to other countries (paying a price for the privilege).

For example, Argentina is now on the verge of collapse. Chile and Brazil have already been affected, other South American countries will be dragged along in the chaos. Yet there are no risk budgets. Governments have not asked themselves what risks they want to take, nor enquired about the cost of transferring risk. Yet, direct hedging is essential in advance of unforeseen crises. The tools have been developed (and there are many more to come); measurement is more difficult but most important. A key task for government is to anticipate the effects of a crisis and to respond pro-actively to the variety of difficulties that may arise.

In this dynamic environment, with

what is risk?

Risk is a confusing term, as John Adams of University College, London, explains in a thought-provoking book[1].Should we take the view of the analyst and insist that we can measure risk only by accurate determination of the probability that an event of given size will occur? Or is risk a subjective judgement of the impact on a particular individual of such an event? Adams quotes use of the term 'detriment' by the 1983 Royal Society study group[2] as what most people mean by risk. It is: "*a measure of the expected harm or loss associated with an adverse event*". It is generally the integrated product of risk and harm and is often expressed in terms such as costs in £s, loss in expected years of life or loss of productivity, and is needed for numerical exercises such as cost–benefit analysis or risk–benefit analysis.

The programme at the Isaac Newton Institute for Mathematical Sciences (see page 9) brought these two perspectives of risk together. Twenty mathematicians expert in extreme value analysis and nonlinear time series analysis reviewed the latest thinking on how to quantify risk in finance, insurance, economics, environmental risk and in business. To challenge this group on how its results might be applied, five one-day workshops were held bringing together the users of risk analysis. The discussion at the final workshop illustrated the gulf between analysts and users. Many companies are derailed by step changes in cash flow caused by economic conditions, sharp changes in commodity prices, an acquisition that turns out to have been over-valued or a loss of confidence in the company's management by the market. Analysts can only go so far in quantifying such risk. Board members often have to make judgements with incomplete information.

In the past, analysts might have fitted a distribution to all the available loss data without taking into account possible underlying differences in or changes to the processes that cause the extreme value or without allowing for the time-dependent behaviour of the distribution parameters. Now, new methods are available which use methods for modelling the tails of distributions[3,4] and which take proper account of the non-stationary behaviour of time series[5].

1. Adams, J, *Risk* (UCL Press, London, 1995).
2. *Risk assessment: a study group report* (The Royal Society, London, 1983).
3. Embrechts, P [ed.] *Extremes and integrated risk management* (Risk Books, London, 2000).
4. Embrechts, P, Klüppelberg, C & Mikosch, T, *Modelling extremal events for insurance and finance* (Springer-Verlag, Berlin, 1997).
5. Fitzgerald, W. J, Smith R. L, Walden, A. T & Young P. C. [eds] *Nonlinear and non-stationary signal processing* (CUP, Cambridge, 2000)

chaos and uncertainty, many regulators and reporters who do not understand that the risk management technology we have in place would suffice to deal with many of the salient events that do occur. The regulators seem always to want to develop new regulations in response to these salient events when the marketplace might more readily devise their own responses. Too much information leads to both less that perfect markets and less than perfect regulation.

The major activities in finance include facilitating transactions among individuals and entities. The objectives may be as different as saving for the future, risk transfer and diversification, financing large projects that cannot be done alone, using market signals to help make decisions and so on. Grafting regulation onto such a dynamic fabric of activity raises the question of how to set boundaries defining the scope of regulation. Many vested interests approach the regulators and say, "we want you to regulate us to level the playing field." My suspicion is that their profits are thereby enhanced over what they would have been if the boundaries had been clearly defined and if people competed within them. ❐

Risk inseparable from business

Dr David Allen

David Allen is Group Chief of Staff and Executive Vice-President, BP plc.

My responsibilities in BP involve planning strategy, process development and organisational development as a way of equipping the company to manage risk. I have done that for the past fifteen years, so that what I have to say is from a practical perspective. But let me say at the outset that transparency of information and data is crucial to risk management.

From a businessman's point of view, risk and uncertainty are not inherently bad. To the extent that they are the basis of competition, they are indeed good. Successful competition requires that an institution should first understand, and then manage the risk it takes. But competition also requires a capacity to demonstrate to various constituencies, not least the owners of the business, that the risk being taken is actually understood: that is governance.

Now for some salient features of risk in the oil and gas industry. It is capital-intensive and used to making large bets; one deep-water exploration well costs about $50 million and the chance of a viable strike is maybe one in five. The revenue streams of oil companies are also subject to other risks, particularly in prices, which are outside our control. Our business involves political risk-management across a range of different countries and regimes. We also have a high technical content, although the risks associated with technical change are less immediate than some of those to which I have already referred.

At BP, our current businesses range from exploration and production (capital-intensive and with a 20-year life cycle) to refining and marketing (also capital-intensive but with shorter life cycles) to quite substantial trading activities. All these activities have different risk profiles, and we have found that the management of these business risks requires a pro-active approach to managing markets, usually by being first movers.

Organisationally, we have found ways to fit entrepreneurship within a large commercial institution. Much of what I want to say has to do with the problem of creating the space for people to innovate, move and actively manage risk while maintaining coherence in a growing institution.

Like other companies, we are subject to both economic and market change. We try to manage that by thinking about the financial robustness of the company on a longer timescale, the duration of the economic cycle for example. We also aim to set up the balance sheet so as to accommodate manageable risk. And we discuss with the board our future financial shape and the nature of the financial risk stemming from market uncertainty.

We are conscious, of course, that it is the unmanageable risk that is commensurate with all the revenue streams of the company. At a succeeding conversation with the board, we may say "This is how we would wish to manage those risks". Everything depends on how we create frameworks that allow us to discuss with the board the nature of the risks we are taking and allows the board to judge whether it believes them to be acceptable.

BP's recent history, is instructive, beginning ten years ago when the company was close to bankruptcy, lost its then Chairman and Chief Executive and cut the dividend. During 1992–97 we focused on three objectives. One was to get the governance of the company right, so we separated the posts of Chairman and Chief Executive and instituted more formalised board governance structures. Another development was to set out clear and simple targets for the company, both internally and externally, making explicit the risks we were taking. Third, we simplified the company by removing many layers of complexity to permit the specific accountability of people for business results.

Phase two, in the recent past, was a period of sectoral transformation. We and many others recognised a need to consoli-

date. We ourselves have been through a period of three or four mergers, with two immediate consequences: the scale of our business has increased by a factor of 2.5, and we have been compelled to grapple with managing the risk of integrations.

If you think of the complexity of trying to put together companies of the scale of BP, Amoco, Arco and Burma Castrol, the risk is that of failing to put them together successfully. What we did was to harvest the skills we had built in phase one — how do you give real focus to the company and provide for real accountability?

In phase three, which is where we are now, we have a much larger company that will grow organically, but which is more widely spread. How must our management and our strategic and risk management models evolve?

There are two key considerations: strategy and governance. Strategy is vital for the management of risk and is a holistic concept embodying both the intellectual framework that underlies the company and also the question of structure and organization. Strategy compels a long view. You need to see where the grain of the business is leading and to seek to understand the nature of the business and competitive environment in which you are immersed. Strategy provides a map, but it must be one that allows for flexibility.

What does that mean for governance? Internally, governance is the ability to create strategy, transparency and appreciate the risks. Externally it is to do with the clarity with which you are able to explain your strategy and deal with expectations, together with clear delegation and distinctive roles for the executive and the non-executive directors. ❐

Risk in the boardroom

Sir Ian Prosser

Sir Ian Prosser has been Chairman and Chief Executive of, Six Continents plc (formerly Bass plc) since 1987. He has served as a non-executive member of a range of companies including BP, Lloyds TSB, Boots and Glaxo SmithKline.

For fourteen years, I was Chairman and Chief Executive of Bass (now Six Continents, having sold our brewery and the Bass name), combining non-executive and executive roles. Although I did A level mathematics, and econometrics was part of my degree, that was long ago and my view of risk is chiefly qualitative, based on experience and gut-feeling. Isaac Newton may not have approved, but I hope to persuade you that this approach is not as hit-and-miss as it may seem.

I have been asked to comment on the non-executive director's attitude to uncertainty and, in particular, on low-probability but high-severity events such as major asset losses or sudden changes in market conditions. I begin by repeating a point made by David Allen: it is imperative that people, particularly equity investors and the media, remember that business is all about risk. It is about balancing the risk of taking certain actions against the less certain benefits that will follow. Success in business is predicated on the assumption that risk can be managed, at least more accurately than your competitors. Yet it is the very uncertainty of business that spurs innovation. Managing uncertainty is as much about realising the opportunities of risk as about limiting potential damage.

What is the relationship between the quantification of risk on one hand and the attitudes of executives and non-executives on the other? The question is tied up with corporate governance and the increasing pressure on non-executive directors. If you ask senior managers about their risk-management capabilities, most will tell you that managing risk is implicit in everything they do. I am sure those managers are genuine in their commitment, but non-executive directors have a different perspective.

If the company is successful, then quite properly the executives receive great praise. If the company is unsuccessful, you can be sure that the non-executives' performance will be put through the mangle by the press as much as the executive directors. Non-executives are no longer corporate adornments.

In many businesses, however, there are risks that non-executive directors can expect management to have quantified and to have reviewed regularly. 'Value at risk' systems are one example of the tools now used. So are the daily measures of the estimated potential change in the market or the realisable value of a portfolio over a given period.

In a different context, Myron Scholes (p. 9) points out that some of these measures do not work if extreme market movements give rise to a lack of liquidity that prevents positions from being closed. So stress-testing is a further means of quantifying these risks. There is little doubt that responsible companies will take great care of the quantitative assessment of any investment project, but quantification is really only as good as management's assessment of the risks, be they related to operations, to countries (and their stability), market or credit risks. There is no substitute for management's knowledge, experience and judgement.

Many years ago, I was given good advice in this context: iterate all the calculations on a major investment or acquisition to find the point where the assumptions show that the investment or acquisition will create no value. This sensitivity analysis should be carried out both for separate risk factors and combinations of them. Executives and, indeed, non-executives can then apply their experience and business

knowledge to the subjective evaluation of the likelihood that the risk factors will yield that result. This is a particularly important test of major investments.

In any well-run company, management will control risk, but now non-executive directors also have to be satisfied that risk management is explicit. After all, a lot of value can be destroyed if a company gets its risk assessments wrong. Marconi is a classic example, and you may remember Bhopal, owned by Union Carbide, now part of Dow. The legal ramifications of the explosion at that methyl cyanide plant continue, as indeed they do with the *Exxon Valdes* oil spillage.

The non-executive director today has to pay great attention both to the requirements placed on him or her by law and, in Britain, to the requirements of various codes such as Cadbury, Greenbury and Turnbull, now combined in the listing rules of the Financial Services Authority.

Turnbull recently widened the responsibility of the board substantially by requiring explicit acceptance of responsibility in company accounts not only for a system of internal control but also for a system of risk management and its periodic review. It is now extremely important that non-executive directors understand the risks that the company faces and the likely consequences if things go wrong. That in turn entails some form of reporting that non-executives can use to monitor what is happening.

I have been talking about non-executive directors but clearly all members of a board carry similar responsibilities, one of which is to understand the risks of the business. It is often forgotten that, although an individual may be managing director of a particular business division, he or she also shares collective responsibility for the whole company. All directors bear a similar responsibility.

Within Six Continents, we have developed a "major risk review process". It starts with the assessment of risk at a fairly low level and moves through each of our business units and up the hierarchy. At the top of a business there is a tendency to believe that the biggest risks will be the most easily visible, which is often true. But failings at a lower level in a company's hierarchy can also entail significant risks. In our business, it is crucial that all material risks should be defined, that their impact is understood and that a process is in place so that both executive and non-executive directors are satisfied that risks are monitored. When failures occur, they must be brought to the attention of senior management and, ultimately, the board.

The response in many companies to the increasing focus upon risk has been to bring non-executive directors more directly into the monitoring process, usually as members of audit committees, environmental committees, health and safety committees and even risk control committees. Committees including both executive and non-executive directors are a fairly new development, but are now commonplace in industries where regulation has had significant impact — the pharmaceutical business, for example.

In my experience, the quantification of risk is most zealously practised in the financial services industry, in commodity trading and in the treasury functions of large companies. Otherwise, most of the country and market risk assessments I have seen seem to use qualitative assessments such as 'high', 'medium' and 'low'. For the time being, that may be the best that can be done.

The question of insurance, or of risk transfer, is primarily a decision for executive management: whether to insure and, if so, for how much. There is much to be said for reviewing losses over a long period and statistically assessing them so as to answer both questions. A company's insurance arrangements can then be adjusted as and when appropriate to reflect changing circumstances. Clearly, the more capable the executives believe that they are in managing risk, the bigger the financial risk a company is prepared to take. Although this is a management issue, non-executive directors do need to understand the basis of their company's policy on insurance.

Finally, I will touch on the risk to a company's reputation. This is an area that is becoming of increasing importance and which non-executives cannot afford to ignore. Research recently carried out by Deborah Pretty of the Oxford Research Institute tracked the share price of some fifty companies that had suffered disasters over a period of two or three decades. She found that prices dipped at the time of the disaster, after which the companies divided into two distinct groups. One group recovered slightly, then fell away as the long-term impact of the crisis took its toll. Companies in the other group were able to recover to their pre-disaster position within thirty days or so, whereafter their share prices continued to improve above their pre-crisis levels.

What these cases show is that managements' ability to manage a crisis can be a valuable asset for the company. The perceived ability to manage a risk can add to shareholder value. So I am ending roughly where I began. Uncertainty produces benefits as well as difficulties. We must continue our search for better means to control risk and increased use of quantitative measures will surely be one of the answers. However, we must also continue to look for those uncertainties which, if properly managed, will offer us great opportunities. ❐

discussion

A major theme was the trend towards control through regulation, rather than leaving risk with individual companies. There are several reasons for this: the culture of blame in which mistakes must never happen; the public inability to understand risk analysis and a growing belief that governments should be able to protect the public from misfortune. Companies sometimes collude with this, thinking it may limit litigation, but more important are the downsides. Ways will always be found around regulation; good companies manage risk over the long term in contrast to the short-term approach of governments focused on the next election; and it is certain that information transfer to governments and regulators will always be inadequate.

Companies' use of mathematical models and cost–benefit analysis can limit or replace the role of regulators. But major risks, such as climate change and inflation, can be managed only by governments. It is vital that both executives and non-executives understand the social, economic and political consequences of governments' taking, or failing to take, action in such areas. It is here that non-executives, with broader experience than executives, can play a big role. Non-executives could also be valuable in managing risks engendered by political and social movements, as faced by Monsanto and Huntingdon Life Sciences.

Finally, it was emphasised that models cannot replace reality. But appropriate use of models can enable companies to take on risks greater than they thought they could carry when relying on hunch or past experience. Or they could have the reverse effect, making companies aware that they were carrying risks greater than they thought they had allowed for.

⇨ ***A detailed summary of the discussion is available on www.foundation.org.uk***

Europe as a global player

The Foundation's Eighth Zuckerman Lecture was delivered on 1 November 2001 at the Institution of Civil Engineers in London by Frau Edelgard Bulmahn, an SPD member of the German Bundestag since 1981 who has been Minister for Research in the German Federal Government since 1998.

Things will never be the same again — that has become a standard phrase since the 11th of September. The world has responded to the terrorist attacks with one voice: the attacks on New York and Washington were aimed not only at the United States of America but at the entire civilised world. As Sir Karl Popper has taught us, we can defend the open society only by fighting its enemies.

But the 11th of September lends urgency to our continuing efforts to build the open society. One part of that task is the continued integration of Europe. We can now see how Europe is taking on new tasks and meeting new challenges. European integration must not be allowed to come to a standstill

European integration within the European Union is not only a matter of money but also of minds. The Eurozone is a necessary first step, but Europe must also mobilise its cultural and intellectual energies, pool its resources — and be alert to what is happening elsewhere. Then we shall be both a strong competitor and a pacemaker in international partnerships. We may even become a model for peaceful co-existence and cooperation.

Global role

Our goal is to make Europe a global player. I will describe the contribution that can and must be made by education and research. Never before have the challenges been as great.

We now demand that scientists develop key technologies for sustainable economic growth as well as concepts for meeting the challenges of demographic change. We expect researchers to provide fresh impetus for combating unemployment and to help manage structural change. We demand progress in disease control and in the development of technologies for coping with natural disasters; we demand that answers be found to the problem of world hunger and that scientists contribute to the solution of social conflicts and of environmental and climate problems. All of us could add further tasks to this list. We also expect our education systems to equip tomorrow's players for success in these endeavours.

What we expect from education and research is nothing less than to shape our future.

Europe can be proud of its recent achievements in research and education. In climate research, from the Earth Summit in Rio in 1992 through to the Climate Change in Kyoto in 1997 and the follow-up conferences in The Hague and Bonn, European research had fostered a common political attitude that has been key to the success of negotiations.

In aeronautical research, the success of Airbus shows how Europe succeeded in catching up with the world market leader in an extremely competitive industry, starting from a seemingly hopeless position.

In the area of information technology, the JESSI project has demonstrated how European companies acquired the necessary know-how and successfully competed in the international marketplace although European chip production lagged far behind in the 1980s.

In higher education, European policy now extends beyond the European Union. The Bologna process has been continued this year in Prague and will reach its next milestone in Berlin in 2003. Thirty-three European countries are participating in a project to re-organise European education by voluntary agreement. The varied opportunities for study in Europe are to be made more transparent and compatible. Ultimately, Europe will be perceived as a single higher education area — from the United States and Asia in particular.

My final example is the ERASMUS programme, which has provided university students in Europe with an opportunity to spend one year at a university in another European country. In the period 2000 to 2006, up to one million students will benefit from this programme.

These examples show that Europe can be a driving force in the world so long as European countries work as a team – a team whose members, the EU member states, play well together while retaining their individual features and contributing their special capabilities. Of course, we want to play in the champions' league, so to speak, and win the World Cup, but we will at the same time observe the rules of fair play and partnership in our cooperation with other countries.

The European Research Area

At its meeting in Lisbon in March 2000, the European Council formulated a new strategic goal for the European Union: by the end of this decade, the Union is to become the most competitive and dynamic knowledge-based economy in the world. For achieving achieve this goal, we need better policies for the information society, a stepping up of the process of structural reform and the modernisation of the European social model. The European Council in Gothenburg recognised, in June this year, that to achieve all this, we need an integrated approach based on the principle of sustainable management.

Education and research are major elements in this process. We need not only modernisation at the European level but action by each member state. In Germany we have made a start. We are reforming antiquated employment law in higher education and public research. We are giving our institutions more responsibility to reduce bureaucracy. We are sharpening the focus of our specialised research institutes to enhance their synergy. We are focusing research on particularly promising areas and we are increasingly providing programme-oriented and project-oriented support. We are supporting the innovation transfer between science and industry and stepping up support for small and medium-sized enterprises. We are

resolved to establish equal opportunities and we will markedly increase the percentage of women professors at universities.

We have faced up to the financial implications of these reforms. For the fourth year running, we have increased the budget for education and research, which in 2002 will be 15.5 per cent greater than in 1998, when this government took office. In the coming year, my ministry will have about DM16.4 billion — the largest education and research budget ever in the Federal Republic of Germany.

We intend to make education and research in Germany more attractive and competitive internationally. Therefore we have increased transborder exchanges of young people, university students and researchers. Our goal is to double the number of university students who spend training periods abroad to 20 per cent.We also want to make German universities more attractive for those young scholars and scientists who are now attracted by the United States and the American research environment.

Because of demographic change, we increasingly depend on young foreigners with special qualifications. We have therefore started to open up and internationalise our study programmes, which is a milestone in the development of German higher education. We have introduced international study courses leading up to Bachelor's and Master's degrees, which are a novelty in Germany. It is now possible for foreign students to begin their studies in Germany and enrol in courses which are taught in English. Germany now offers an international environment for teachers, students and researchers.

Transborder cooperation in education is not aimed at harmonising the different educational systems in Europe, but at fostering productive competition between them. Cooperation between the member states will encourage all countries to examine the strengths and weaknesses of their education systems, try new approaches and add to the common features in Europe. We need agreement on common educational policy goals and on international quality standards. In my view, we must learn from each other more systematically and provide a basis for such learning by the comparison of performance.

Research focus

The question of what research topics must be addressed jointly to ensure Europe's international competitiveness is, I think, the key question. We are currently debating within the European Union the draft of the Sixth Research Framework Programme, its content, structure and budget. The Sixth Framework Programme is our main tool in establishing a single European research and innovation area.

Here are some of the challenges that can be met only by joining forces at the European level:

- Control of diseases of modern civilisation by means of Europe-wide clinical studies and research, for example on BSE and other TSEs.
- Common standards and methods for monitoring food safety.
- Making sustainability the guiding principle of all business and management.
- Safeguarding our energy supply in the long term by making greater use of renewable energy.
- Overarching solutions for traffic guidance systems and an infrastructure for a transport system based on hydrogen.

But we also need an environment more favourable to the rapid conversion of research results into marketable products. For example, we need:

- A common European patent including a grace period;
- To link research institutions by means of a high-performance network for data exchange;
- Joint databases and archives of model organisms;
- Uniform provisions governing the examination and release of genetically modified organisms.

Supranational research organisations

The concept of the European Research Area (which is central to the Sixth Framework Programme) raises questions about the the future of the many organisations, such as CERN, ESO, ESA and EMBL, which are already pan-European. My personal view is that we should consider whether they should continue to operate in their present form. It is possible that reforms would yield new synergies and reduce costs. The imminent accession of new members to the Union seems to make a review of these supranational European research organisations advisable.The planned accession of the United Kingdom to ESO has revealed what problems need to be solved.

I believe we would be well advised to pursue, in the medium-term, the goal of making the supranational research institutions agencies of the European Union, with funding through national EU contributions. Already there is ongoing cooperation between the EU and ESA. I look forward to the response of the research community.

Ethics and the life sciences

More than any other field of research, the life sciences are present an emotional and intellectual challenge now very much on people's minds. This is why the British Parliament's decision to permit the production and use of embryos for therapeutic research has provoked such a response. This decision, together with that of the US President that public research money would be used exclusively for work with stem-cell lines already available, has given new impetus to the public debate. Today's dramatic developments in science and technology affect every sphere of life; some people in the United States believe that human beings themselves will soon become the subject of biotechnological reconstruction.

When we talk about building Europe, we mean not only the establishment of a common foreign and security policy, the internal market or the European education and research area, but we also mean the provision of a sound basis for building an ever closer union. For centuries, Europe has been united by common cultural and intellectual traditions. Over a long period of time, a set of common European values has developed which unite us across national borders. The further development of these values is at the heart of the debate about the opportunities and risks of genetic engineering.

We must seize the opportunities offered by biotechnology, but we must also weigh the risks and — if possible — avoid or at least minimise them. In this bioethics debate, I support differentiated thinking and action. Let me explain what I mean. In view of the values embodied in the German constitution, the limit, I think, must be set where embryos are to be produced specifically for research purposes, and even more so where germ-line manipulation and reproductive cloning are concerned.

In my view, we must further intensify the exchange of views on these problems as Europe grows together. On the basis of our common values, it should be possible for us to reach agreement. But we should also ask ourselves whether these issues should remain national concerns or whether they should become a European responsibility.

Fifty-four years ago, in Zurich, Sir Winston Churchill predicted that "If Europe were once united in the sharing of its common inheritance, there would be no limit to the happiness, to the prosperity and the glory which its three or four hundred million people would enjoy." Collaboration in education and research could yet achieve that goal. ❑

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Mr Pete Goss MBE, Chairman, Goss Challenges
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24 April, 2001

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Professor Morris Brown FMedSci, Professor of Clinical Pharmacology, Addenbrooke's Hospital and University of Cambridge
Professor Paul Elliott FMedSci, Professor of Epidemiology and Public Health, Imperial College of Science, Technology and Medicine
Professor Rob Pickard, Director General, British Nutrition Foundation
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30 May, 2001

Genetic Databases – Threat or Opportunity?

The Lord Oxburgh, House of Lords Science and Technology Committee
The Baroness O'Neill of Bengarve CBE FBA, Newnham College
Dr Peter Goodfellow, GSK
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Professor Brian Heap FRS, The Royal Society
Professor Dominique Dormont, CEA (Fontenay), France
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Nick Millard, Project Director, Autosub Project: Southampton Oceanograpy Centre
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Mr John Williams FNI, General Manager, Boyd Line Management Services Ltd
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5 February, 2002

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