"The Idea of Risk and its Relevance to Genomics"

by
William Leiss, FRSC
NSERC/SSHRC/Industry Research Chair in Risk Communication & Public Policy,
Haskayne School of Business, University of Calgary;
Professor, School of Policy Studies, Queen's University;
Executive-in-Residence, McLaughlin Centre for Population Health Risk Assessment,
University of Ottawa
1 Steward Street, Room 308
Ottawa, ON K1N 6N5
(613) 562-5800, x2116
wleiss@uottawa.ca
http://www.leiss.ca

Presentation to the
GE³LS Winter Symposium
6-8 February 2003
Montréal, Qc

Friday, February 7, 2003: "Genomics, Risk, Science and Acceptability"

William Leiss: "The Idea of Risk and its Relevance to Genomics"

Abstract

In this paper I use the concept of risk to provide a suitable canvas on which to array and describe – in a systematic manner – the social, ethical, and legal issues raised by the engineering of genomes by direct manipulation of DNA ("genomics"). I do so because the concept of risk has certain intrinsic attributes which make it especially useful for this purpose. In the first place, risk poses the two questions that are of greatest interest to everyone, in terms of outcomes – of either natural or technological processes – that cause concern or dread to individuals and societies. These are: (1) How likely is it to happen? (2) If it does happen, what are the expected consequences? In the second place, risk lends itself to both qualitative and quantitative description. In both types, but especially the latter, risks can be compared with each other, across very broad domains, thus facilitating certain critical choices open to us – in particular, whether certain risks rise above the threshold of acceptability or tolerability, whereas others do not. Third, the concept of risk asks us to estimate the dimensions of the uncertainties that are attached to particular risky ventures, so that we know whether the risk can be controlled with the strategies that are currently available to us.

Against this background I give a preliminary characterization of both the intrinsic and extrinsic risk factors associated with genomics. The paper concludes with a plea directed to all active researchers in this area, most definitely including the molecular biologists, to participate actively, now and continuing into the future, in the process of refining these preliminary characterizations. The reason for this is straightforward: Our capacity to engineer genomes is perhaps the most fateful of all human powers, in that the risks to be managed go beyond specific interventions, and reach into the very foundations of human civilization. Therefore we must be proactive in managing these risks, acting in a precautionary mode, rather than waiting for consequences to emerge before doing so.

1. Preface.

Today I have eschewed the normal PowerPoint presentation in favour of an old-fashioned lecture, which asks you only to listen carefully and consider your objections to my arguments. In doing so I return to my origins, where my highest degree is in philosophy, and making good arguments is what we philosophers are supposed to be able to do. I list here the main points I will make, so that you can keep them in mind as I elaborate on them:

1. Risk is a powerful concept that defines the trajectory of industrial society, intent on the domination of nature for enlarged human benefit, a project envisioned by Francis Bacon in the 17th century.

2. We seek to carry out this project in two interconnected ways, (a) by maximizing the spread between benefit and loss, and (b) by minimizing the "downside risk," i.e., protecting ourselves from the possible worst-case consequences.

3. Good risk management requires us to recognize the pertinent risk factors in a particular endeavour in advance, and failure in this regard can be catastrophic; I give examples of different types of such failures.

4. Our capacity to engineer genomes is perhaps the most fateful of all human powers, in that the risks to be managed go beyond specific interventions, and reach into the very foundations of human civilization.

5. Society can manage genomics risks only if the scientific community becomes actively engaged in this process, assuming its share of responsibility for their potential scope, well in advance of successfully achieving our practical objectives.

2. Interlude: First Story.

I begin with a story. Almost two centuries ago a young woman engaged in a parlour game with her traveling companions, including two rather famous English gentlemen by the names of Byron and Shelley. She bore the name of her mother, the famous feminist Mary Wollstonecraft, who died shortly after giving birth to her; but the world knows her by her married name: Mary Shelley. The game – played while the three of them were vacationing in Switzerland – was to write a gothic novel, and of the three she was the only one to carry it out. The result was *Frankenstein,* first published anonymously in 1818; she was all of nineteen years old when she wrote it.[1]

Most people know her achievement only through the equally famous movie, starring Boris Karloff. This is a shame, because although it is a remarkable work of art in its own right, James Whale's 1931 film does not do justice to Mary Shelley's genius. Even her subtitle is important: *Frankenstein; or, the Modern Prometheus.* Prometheus, in Greek mythology the god who stole fire from Heaven and gave it to mankind, and who was punished by Zeus by being chained to a rock, where an eagle fed on his liver, which regenerated daily so that his torment was endless. Even her novel's epigraph is important, three lines on the title-page from Milton's *Paradise Lost* where Adam is addressing God:

> *Did I request thee, Maker, from my clay*
> *To mould me Man, did I solicit thee*
> *From darkness to promote me…?*

Mary Shelley's extraordinary far-seeing genius is summed up in the fact that her novel is more "relevant" today than it was when she wrote it. Her main theme is about the responsibility of scientists for their creations. Her narrative tells how Dr. Victor Frankenstein abandoned his creation – the world's first recombinant entity – at the moment of his coming alive. He fled in horror from his laboratory, forcing his creation

[1] There is an excellent commentary by Harold Bloom in the Signet Classic edition (New York: Penguin Books, 1983), and a full contextual analysis in Susan J. Wolfson's recent edition (New York: Longman, 2003).

to go into the world alone. There is immense pathos in her rendition of the creature's fate, for he thinks of himself as human, and yet every encounter with humans is disastrous, for like Victor they flee from him in fear and disgust. (It is significant that he has no name, of course.)

So he hides out, in proximity to the humans who have spurned him, reading Milton and eavesdropping on the players of classical music. His encounters with humans lead to what are really accidental tragedies, but humans regard him as a murderer and hunt him. Meanwhile Victor flees to Scotland, where his creation tracks him down and confronts him with a simple request: You made me, therefore take responsibility for my fate. Humans will not accept me as one of their own. I am dying of loneliness; you must create for me a female mate of my own kind. Victor refuses, expressing horror at the very thought, and his creation proceeds to wreak terrible revenge upon him.

3. The Modern Idea of Risk.

An orientation to the world where systematic risk-taking is the norm rests upon a more fundamental notion, namely, that the world of nature is essentially a field in which human ingenuity can be exercised without restriction. The phrase "without restriction" is crucial: It means that there are no other interests subsisting there, no other entities possessing a will and consciousness – no gods or spirits or demons – that can oppose us with an alternative plan as we proceed to manipulate nature to our benefit. This world is simply full of latent "power" (what we now call matter – energy) that can be appropriated and turned to human benefit. The traditional competitions among people within society are zero-sum games, where gains are won only at the expense of others. But the contest with nature is different, because there are no competing interests.[2]

[2] This is Francis Bacon's idea. See W. Leiss, *The Domination of Nature* (1972, reprint edn., Montréal: McGill-Queen's University Press, 1994), ch. 3.

Victory – conceived as understanding natural laws so as to manipulate natural forces – yields an endless and accelerating stream of net benefits.

The concept of risk has certain intrinsic attributes which make it especially useful for organizing our appropriation of nature. In the first place, risk poses the two questions that are of greatest interest to everyone, in terms of outcomes – of either natural or technological processes – that cause concern or dread to individuals and societies. These are: (1) How likely is it to happen? (2) If it does happen, what are the expected consequences? In the second place, risk lends itself to both qualitative and quantitative description. In both types, but especially the latter, risks can be compared with each other, across very broad domains, thus facilitating certain critical choices open to us – in particular, whether certain risks rise above the threshold of acceptability or tolerability, whereas others do not. Third, the concept of risk asks us to estimate the dimensions of the uncertainties that are attached to particular risky ventures, so that we know whether the risk can be controlled with the strategies that are currently available to us.

On this foundation is built the idea of risk-taking that, beginning in the 17th century, gave rise to industrialism and the technologies we use today.[3] The core idea is simple: If a way could be found to first, estimate risk quantitatively, and second, to spread it among a group in proportion to expectations of benefit (self-interest), more risk-taking activity, and thus potentially more collective net benefit, will result. Net benefit, or securing a long-term excess of gains over losses, is thought to be the fundamental rationale for intelligent risk management. But limiting exposure to loss is even more fundamental, for it turns out that for most people avoiding an unacceptable level of loss is much more important than securing gains.[4] Estimating the likelihood of future

[3] Peter L. Bernstein, *Against the Gods: The Remarkable Story of Risk* (New York: Wiley, 1996).

[4] This is Daniel Kahneman's and Amos Tversky's famous "prospect theory," where experimental results show that people are most strongly motivated by loss aversion: see Bernstein, ch. 16. Kahneman won a 2002 Nobel Prize for his work in decision theory.

adverse outcomes based on patterns of past events, using statistics and probabilities, then pooling the risks, enables insurers to protect most individuals and firms from crippling losses that otherwise would prevent them from continuing to engage in risk-taking (and wealth-generating) activities.

In other words, in the first instance the risk calculus is preoccupied with putting bounds on the chance of loss. "Controlling the downside risk" – or, in technical language, seeking to minimize exposure to the maximum loss – is recognized as a basic strategy in game theory, where it is known as the "maximin" strategy (choose the least bad worst outcome).[5] Once having limited the downside risk, entrepreneurs can engage in aggressive risk-taking activity, seeking to maximize net benefits to themselves and (via the Invisible Hand) also to society. So risky behaviour moves imperceptibly from preoccupation with loss to a focus on accumulating a surplus of net benefits.

My final general observation is that the scope or scale of benefits sought, on the one hand, and the risks run in order to claim them, on the other, are roughly commensurable. By "benefits" I mean the things and techniques of value to us that can be created out of matter and energy through our technological manipulations of nature. The scale of benefits increases in proportion to the range and subtlety of those manipulations; we might call this a basic law of technological progress. In addition, the *ratio* of benefits to disbenefits (unintended side-effects or harmful externalities) increases, often dramatically, as knowledge grows. Earlier technologies are like blunt instruments which can cause a good deal of collateral damage as we create value with them; later ones tend to be more efficient and precise in terms of realizing our goals and minimizing costs.

---

[5] This strategy was first known as "Pascal's Wager": see W. Leiss, *In the Chamber of Risks: Understanding Risk Controversies* (Montréal: McGill-Queen's University Press, 2001), pp. 261-2.

Yet all powers are two-edged swords. As the scope of the good they can do for us expands, so does that of the harm they might do, either inadvertently or by someone's deliberate choice. Two examples must suffice. Unlocking the power of the atom yields a new energy source and a fearsome new weapon of mass destruction at the same time. The technique of "DNA shuffling" and the creation of "daughter genes" makes possible the creation of new biological traits – as well as the possibility of so-called "synthetic pathogens" and the prospect of confronting novel infectious diseases against which no immunity exists.[6]

A simple lesson flows from this perspective. The challenge of managing effectively the risks we create – to ourselves, other creatures, and ecosystems – in the search for human benefits grows in proportion to our technological prowess. Managing risks means adopting a precautionary mode of behavior, trying to identify and limit potential trouble before it hits us in the face. We have a collective responsibility – an ethical duty, if you will – to act in this way. Yet, quite obviously, discharging this responsibility is easier said than done and gets harder with each passing day. This is so because the global reach of innovation demands effective international collaboration in managing risks, a capacity which presently exists at a primitive stage of development.[7]

4. Risk Management.

The purpose of risk management, as first developed in the financial sector and later extended into the health and environmental zones, is to bring a systematic perspective to bear on the propositions already enunciated. Another way of saying this is to recognize that through risk management we seek to introduce a foundation of

[6] Carina Dennis, "The Bugs of War," *Nature,* vol. 114 (17 May 2001), pp. 232-5.

[7] The best example is the fate of the International Convention on Biological and Toxic Weapons, which came into force in 1974 but remains a "dead letter" because it has no inspection and verification protocol. Full information is available at: http://www.bradford.ac.uk/acad/sbtwc/ .

precaution beneath our risk-taking activities. This occurred first in the domains of public health and of occupational health and safety. The introduction of sanitary measures to control the spread of infectious disease is an attempt to head off the adverse consequences, or at least a certain proportion of them, before they arise. Establishing allowable limits of exposure to hazardous substances in the workplace is an alternative to ignoring the casualties and just replacing sick workers with others not yet sick, without bothering to ask whether it was the workplace that sickened them.

The management of health and environmental risks, considered as a precautionary exercise, developed as a step-wise procedure for controlling risk:

1. Hazard identification and characterization, specifying all relevant possible adverse outcomes (population average *and* subpopulations, e.g. gender- and age-specific), including a dose-response curve;

2. Exposure estimation, often using surrogate data;

3. Risk assessment, as probabilities of occurrence for each adverse outcome and relevant subpopulation, identifying uncertainties;

4. Risk reduction strategies, where probabilities are above the level of "tolerable" or "acceptable" risk;

5. Risk management options: risk-risk, risk-benefit, risk-cost-benefit trade-offs;

6. Monitoring and evaluation of new data.

Advances in methodologies for toxicology, epidemiology, and statistical analysis have been one of the primary drivers of progress in this area. In this respect risk assessment resembles detective work, where the "culprit" sought is the significant association between risk factor and adverse outcome than can be deeply hidden, especially in epidemiological data.

To be sure, these "technical" aspects of the risk management approach are only one side of the whole story, for there are important social interests that can be affected by it. Risk is unequally distributed in many ways – in occupations, socio-economic levels, neighborhoods, race, and other ways –, bringing matters of justice, equity, and equality to the fore. Risk is also unequally distributed as a result of idiosyncratic variations in personal proclivity (degree of risk aversion) and preferences or choices. This means that very important dimensions of health risk can be, at least in principle, under substantial personal control – affected by personal choices in patterns of diet, exercise, intake of alcohol and other drugs, recreation, driving behavior, tobacco smoking, and many other domains. In addition, people can perceive the nature and significance of many hazards, especially those which they believe are being imposed on them without their consent, in terms that are radically opposed to those who are using formal methodologies to perform quantitative risk assessments.

So bitter battles over risks can erupt and have done so regularly. These battles began a century ago with respect to occupational risks. Firms routinely denied that there was sufficient cause-and-effect proof (using a legal standard of proof) to justify lowering allowable exposures, since expenses were incurred in doing so. Evidence often was hard to come by, and in many cases was concealed when it surfaced. Few cases are as notorious and long-lasting, or as fraught with catastrophic health consequences, as that of occupational exposure to asbestos, which goes on to this day. The history of occupational risk is important for showing us that social and economic interests come into play whenever changes are sought to the prevailing community standards for acceptable levels of risk.

In public health no battle has been as bitter as that with the tobacco industry, which fronted the longest-running battle against epidemiological science that has ever been waged. At its height in the 1980s and 1990s, before the industry finally capitulated, specialists were recruited with secret payments to cast doubt on epidemiological

studies.[8] More recently, the perceived economic costs of complying with greenhouse-gas emissions reductions targets, to control the risks associated with climate change, resulted in attacks on the credibility of the scientists who support the reports of the Intergovernmental Panel on Climate Change. Science itself, as represented by toxicology and epidemiology, is drawn into fray when controversies erupt among social interests about risk assessment and management.[9]

Risks associated with the engineering of genomes, especially the human genome, will without a doubt be intensely controversial, and the scientists working in those areas will be drawn into those controversies, along with the rest of us.

5. Interlude: Second Story.

This is an account of a personal encounter I had recently with an eminent neurobiologist. His area is the biology of memory, in particular, the neurological process by which short-term memory is converted into long-term memory. As in most other respects, the processes in the human brain are similar to those in other mammals, including those which most people would regard as "lower" life-forms. In his animal research he discovered the specific neurological pathway and biochemical mechanisms through which the conversion referred to takes place. He also discovered that the process is controlled by one specific gene, both in other animals and in humans. When the gene was switched off in a test population of laboratory mice, the resulting deficit in neurological performance was confirmed. The long process of research which had culminated in this proof was painstaking, original, and brilliantly executed.

[8] This ugly episode is related and documented in Stanton A. Glantz *et al.*, *The Cigarette Papers* (Berkeley: University of California Press, 1996), ch. 8.

[9] For an overview see Leiss, *In the Chamber of Risks: Understanding Risk Controversies.*

An inability to convert short-term to long-term memory is a serious matter for any animal. (As in many other cases, the consequence of this deficit in humans was discovered in an actual case, where a section of a person's brain had been removed in order to control severe epileptic seizures.) In effect, it means that learning is impossible: Each day's experiences will present themselves to the creature as entirely new, so what is learned that day cannot be stored and called up again. Any wild animal with such a deficit will have diminished survival outcomes. After the lecture I introduced myself to the speaker along these lines: "I'm a public policy specialist, not a natural scientist. This is an extraordinary discovery. What bothers me is that someday, someone might want to switch off this gene deliberately in some humans."

Why raise such a ridiculous idea, you say? Well, for a couple of years now I've become obsessed with terrorism risk and rogue science, especially in the area of molecular biology. It seems to me that this is an area of science and technology which is especially relevant to such applications, because of its inherent simplicity: Soon, if not already, gene manipulation with simple organisms, such as bacteria and viruses, could be a backyard-garage type of operation. (In this it differs from nuclear and chemical technologies, which require elaborate installations.) And, as science progresses, moving up to other animals and humans should be feasible. There is no effective international control against such risks, especially after the USA shot down the draft implementation and verification protocol for the International Convention on Biological and Toxic Weapons.[10] And the ideology we have come to know as "fundamentalism," as represented today in al-Qaeda, has made it clear that all such weapons will be part of its palette.

[10] The whole sad story is told at: http://www.bradford.ac.uk/acad/sbtwc/ . The rationale for the US position is that the intellectual property of its biotechnology industry could be compromised.

So that's why I posed this issue for our eminent neurobiologist. He was, to be sure, a bit taken aback at first, but then he replied: "Yes, I suppose that might arise. But that's a problem for people like you to solve." The implication was clear: He was not going to be a part of the solution. I requested a further discussion at the reception that followed, but unfortunately it did not take place.

6. Risk Factors associated with Genomics (Genetic Engineering of DNA).

Considered simply as an area of scientific investigation having practical applications for human benefit, molecular biology is an immensely important field of inquiry. In particular, the sequencing of complete genomes and (ultimately) what will follow – full knowledge of individual gene functions, gene expression mechanisms, and the pleiotropic effects of gene alteration – will have nothing less than revolutionary consequences for us. And these steps will introduce us to a range of risks which we have never before confronted. At present, I think, we do not know even where to start in confronting them.

For there are some types of downside consequences associated with genomics which, if they come to pass, will have one of two results: Either they will produce catastrophic harms or they will so frighten the population that there will be a demand for an end to research and development in this area. Or both.

The term "risk factor" connotes a probable cause of an adverse effect, taking into account not only varying degrees of uncertainty, but also the fact that risk is by definition probabilistic. When one says, for example, that tobacco smoking is a risk factor for cancer (lung, mouth, pharynx, larynx, esophagus, pancreas, uterine, cervix, kidney, and bladder) and dozens of other diseases, it means (a) that the existence of an association between the two is highly plausible, (b) that a scale of harmful dose is known, and (c) that a certain percentage of smokers will fall victim to these diseases.

About 10% of regular smokers will get lung cancer, on average, but the distribution of the risk is also very important: Women have double men's risk of lung cancer, and are at risk for more serious type of this disease, at an equivalent dose.[11] This terminology is very widely used and is relatively easy to communicate, despite the fact that there are some residual difficulties in understanding.[12]

The term "risk factor," then, has to do with adverse consequences only and thus begs the question as to what benefits accrue as a result of the risk-taking behavior. As a general rule we can assume that risks in this sense are encountered as a result of the search for benefits, even with something like smoking. A fair description of a risk domain, therefore, requires a sketch of both benefits and costs (where costs are the probabilities of harm, or risk factors), and both sides of these equations may be phrased in either monetary or non-monetary terms.

Risk factors for technologies can be sorted into two categories; for want of better terms I shall call them "intrinsic" and "extrinsic." In the former I place those hazards which are inherent in either the nature of the technology itself or in its normal applications. To give an example from the world of chemicals: trihalomethanes and their cancer risk are created as byproducts of using chlorine to disinfect water. The occupational hazards associated with producing chlorine, or the risk of accidental releases to those who live in proximity to the plant boundary, are other examples of intrinsic risk factors. "Extrinsic" refers to the impacts that specific technologies can have on a wide range of institutional subsystems in society – law, ethics, religion, and politics.

[11] http://news.bbc.co.uk/1/hi/health/2542725.stm ; http://www.womenof.com/Articles/hc0117002.asp

[12] Saying "smoking is a risk factor for lung cancer" can be confusing to some people because it is not the only risk factor for this disease, although it happens to be overwhelmingly the predominant one. The statements (1) "smoking accounts for 30% of cancer deaths," (2) "10% of regular smokers will get lung cancer," and (3) "smoking causes 75-85% of lung cancers," are all accurate.

In what follows I will attempt here only a partial list of the two broad categories of risk factors and benefits associated with the engineering of genomes through the direct manipulation of DNA. I ask the members of the audience, and the Canadian genomics research community more broadly, for help in creating a complete and accurate list. The reason for this is simple: As a society we need to have as accurate an idea as possible about the nature and scope of the hazards we face in this domain. Equipped with this idea as well as with the precautionary approach, we would then be in a position to engage a wider public in a discussion on how to manage the associated risks. My plea to you is this: *We must do this now, proactively, and not wait to be confronted with the actually existing harms*.

In order to do such a sketch, we must be clear about what is the scope of the "power over nature" that genomics science seeks. Altering smaller or larger sections of the genomes of existing entities (plants, animals, humans), in order to achieve human benefits otherwise unattainable, is what most people would think of right away. But there is a much larger prize lurking in the background: creating *de novo* the biological "platform of life" onto which any desired set of traits whatsoever could be grafted. This is known as the "minimally necessary genome" and it is now a prize being sought, by – among others – the irrepressible Dr. Craig Ventner of the Human Genome Project fame:

> Scientists in the United States plan to build a tiny new germ from scratch, promising it will be harmless to people and could someday be used to produce new forms of energy. The scientists … want to keep portions of their work secret to prevent terrorists or hostile nations from using the new organism to make biological weapons. If the experiment works, the synthetic germ would begin to reproduce on its own.

A Stanford University bioethicist was quoted as saying that she wasn't too worried by this project "partly because I have a sense that the scientists are aware of the possible risks of what they're doing."[13] I for one certainly hope so.

[13] Brad Evenson, "U.S. scientists aim to build new life in a test tube," *National Post,* 22 November 2002, A3.

A general description of the two distinct classes of risk factors associated with genomics might be as follows: Intrinsic risks arise inevitably out of achieving the ability to undertake genetic alterations in existing genomes, or to construct entirely new genomes, with predictable and reliable results in achieving the expression of desired traits. Extrinsic risks are the impacts that this ability almost certainly will have on a wide range of institutional subsystems outside the bounds of scientific discovery itself – law, ethics, religion, and politics, including such things as the concept of the person and the family.

Again, I request your help me in compiling the full list of risk factor within these two categories, to make it as accurate and complete – from a scientific standpoint – as possible. We must also make an effort to describe the risk factors in terms that are understandable to the public.

Once this is done, undertaking three important tasks will become feasible: First, engaging the public in an informed and sustained dialogue about risk management options. Second, identifying the areas where proactive, precautionary risk control measures should be instituted by researchers and research sponsors, such as funding agencies. Third, identifying the areas where changes in law and regulations are needed.

A simple and familiar example of this typology is provided by the case of genetic screening. Here the benefits include taking precautionary health measures, adjusting one's lifestyle with the knowledge of special risk factors, and making informed choices about mating and reproduction. The intrinsic risk is the psychological damage that could be done to an individual by the gaining the knowledge that he or she is carrying certain types of defects which carry the "sentence" of premature death, or debilitating disease, or social stigma. The extrinsic risk is the possibility that adverse effects will follow from others gaining access to this knowledge: effects on private health or life

insurance coverage, employment prospects, and on judgments made by others about one's suitability as a mate.

6A. Intrinsic Risk Factors in Genomics: Provisional List.

Types of intrinsic risks inherent in any technological intervention – using products of industrial chemistry, say, or DNA manipulations – are, by definition, closely tied to the benefits we seek in making that intervention in the first place. For example:

1. Gene therapy:
   Benefits: control of inherited disease in individuals.

2. Germline gene therapy:
   Benefits: elimination of inherited disease in populations, such as the so-called "French-Canadian variant" of Leigh's Syndrome.[14]

3. Gene enhancement (physical traits):
   Benefits: enhance athletic performance, endurance, skills, etc. in individuals.

4. Genetic modifications of behavioural traits:
   Benefits: control or elimination of anti-social behaviour (e.g., criminality, aggression) in individuals.[15]

Illustrative list of **intrinsic** risk factors associated with the above set of manipulations:

1. Minor unintended adverse genetic and health consequences, resulting from pleiotropic effects;

2. Major unintended adverse genetic and health consequences, resulting from pleiotropic effects;

3. Unintended germline effects in individuals;

---

[14] http://www-genome.wi.mit.edu/media/2003/pr_03_leighsynd.html ; Carolyn Abraham, "Rogue gene found in rare Quebec illness," *The Globe and Mail,* 14 January 2003, A1, A8.

[15] Stephen Scherer (University of Toronto), "The Human Genome Project," presentation to the Queen's Public Executive Program, 1 October 2001, "Twin Studies of Personality Traits," showing the possible proportion of genetic factors in explaining various personality traits and outcomes in specific populations: e.g., "adult criminal behaviour (50-67%)." The importance of this way of representing genetic contributions to behaviour lies in the policies that society may adopt on the basis of what governments *believe* about the possibility of influencing outcomes through genetic interventions.

4. Unintended behavioural consequences.

6B. Extrinsic Risk Factors in Genomics: Provisional List.

Extrinsic risks are the impacts that this ability almost certainly will have on a wide range of institutional subsystems outside the science itself – law, ethics, religion, and politics. An illustrative list of **extrinsic** risk factors associated with the above set of manipulations is:

1. Discriminatory or perverse distributional effects in society of gene therapy and gene enhancement resulting from social differentiation (impacts on differences in income, wealth, race, employment, health, etc.);

2. Possibility of creating isolated genetic sub-populations designed to restrict genetic advantages within certain socio-economic groups and nations;

3. Unintended or intended germline changes through private choices that spread into the wider population;

4. Manipulations of behavioural traits imposed on individuals or groups by governments.

7. Difficult Choices: An Illustration.

Using the concept of risk helps us greatly, I think, to array systematically the risk factors involved in genomics. But of course it does not, and cannot, yield a simple decision rule to resolve difficult matters of judgment in this area. A good illustration of these difficulties is supplied by the matter of therapeutic cloning. Two opposing interpretations of the risk and benefit trade-offs here have been given by members of the academic community in Canada in recent weeks. Tim Caulfield made the case for permitting this form of cloning in the context of Bill C-13, arguing in effect that the future health benefits are substantial and that the downside risk could be controlled by effective regulation.[16]

[16] "I smell a cloned rat," *The Globe and Mail,* 4 January 2003, A15.

More recently, Françoise Baylis and Jocelyn Downie argued the opposite case, saying that the health benefits may be achievable in other ways and that the downside risk is too great.[17] The difference between the two views is largely in the conception of the nature and the scope of the downside risk. For Baylis and Downie permitting therapeutic cloning will make human cloning more likely, because it will generate technological advances in the art of mammalian – and thus human – cloning generally. This is an excellent beginning for an informed debate, which must be pushed further. For example, as between these two cases I believe that Baylis and Downie have the more persuasive argument at present, largely because the regulation proposed by Caulfield would hold sway only in Canada, whereas the techniques perfected by Canadian researchers would become the property of the global community, where no regulation is even imaginable at this point in time.

A recent news item contained this report:

> "A respected Chinese scientist … Lu Guangxiu, 61, who heads a team of 60 scientists at a high-tech laboratory in Changsha, south central China, said last week she had created more than 80 embryos containing the genetic blueprint of an existing adult.... Lu also disclosed that she had created cultures of human cells capable of proving "spare parts" for a variety of fatal human diseases…. In four cases, the embryos have been kept alive to the stage where they are clusters of hundreds of cells and would normally be transferred to the wombs of mothers if they were being used to create babies.[18]

Unless and until effective international regulation of molecular biology applications is a reality, the precautionary approach suggests that therapeutic cloning should be prohibited by law in Canada, and that Canada should press the international community to establish appropriate and enforceable safeguards against human cloning.

---

[17] "Cloning for stem cell research unnecessary and dangerous," *The Hill Times,* 3 February 2003.

[18] Lois Rogers (Times of London), "Chinese claim first human embryo clone," *The Calgary Herald,* 26 January 2003, A6.

8. Conclusions.

Genomics gives rise to types of both intrinsic and extrinsic risks that are unique as well as exceptionally "potent" for individuals and societies. Some of the reasons are as follows. First, both the potential benefits and the risks touch upon aspects of life that are at once intensely personal and private and, at the same time, crucial to social interactions. These include most of the factors which are thought to be important for individual happiness and social acceptance: appearance, pleasing personality, health, sociability, intelligence, attractiveness to mates, fecundity, livelihood, and on and on.

Second, genomics risks touch upon aspects of life that are fundamental to social organization: the concept of personal responsibility in law and religion, an individual's autonomy with respect to her parentage (the "accidental" character of genetic mixing in animal reproduction), the character of political freedom (the development of the "free" individual unconstrained by genetic heritage), and the great values of democracy: justice, equity, and equality.

Certainly the attained level of genomics science and technologies does not give rise to any of these risk factors today. However, what is important – given the sensitivity of these types of risks – is that we look ahead to the capabilities that are undoubtedly sought-after now, and almost certain to be achieved in the future. The types of possible impacts in this domain are not those for which remediation after the fact is appropriate. On the contrary, the potential consequences inherent in these types are such that we must resolve to deliberate and act in a precautionary way, so as to prevent certain types of consequences from ever arising in the first place.

Such deliberation must start within the academic community, where issues are clarified and posed in an appropriate way. Then, of course, it must move out to the public

domain, where credible information resources should be provided to the public well in advance of engaging citizens in prolonged dialogue.

Finally, society can manage genomics risks appropriately only if the scientific community becomes actively engaged in this process, by assuming its share of responsibility for their potential scope, well in advance of successfully achieving the practical objectives stemming from research. To start with simple matters, working scientists in molecular biology need to be out in force at meeting such as this. When one separates the communities of experts in the usual way – where media reports about scientific discovery elicit passing comments from a few "ethicists" –, the results are utterly unsatisfactory, because the two rarely or never engage each other in public dialogue. In my opinion, the practitioners of genomics science run enormous risks of their own if they fail to take up this challenge.

Thank you for your attention.