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Mr Elton Humphery
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Dear Mr Humphery,

Re: Legislative responses to recommendations of the Lockhart Review

Thank you for the invitation of September 18th to make a submission to the enquiry.

Please note that I make this submission in a private capacity and not in any other role. I particularly do not want an association made between this submission and my membership of various Commonwealth and State Government Committees or with those to whom I am engaged as a consultant.

This submission expresses concern about the proposals contained in the PROHIBITION OF HUMAN CLONING FOR REPRODUCTION AND THE REGULATION OF HUMAN EMBRYO RESEARCH AMENDMENT BILL 2006 proposed by Senator Kay Paterson. Similar proposals have been made in a Bill proposed by Senator Natasha Stott Despoja. I have addressed my remarks to Senator Patterson's Bill because it would appear that the issues are much the same.

1. The Bill

Senator Patterson's Bill proposes that the following activities that are now unlawful may be become lawful if approved by the NHMRC Licensing Committee (in accordance with legislated criteria) and that the activity is undertaken in accordance with a licence issued by the authority. A person may be granted a licence to:

a) create human embryos other than by fertilisation of a human egg by a human sperm, and use such embryos;
b) create human embryos (by a process other than fertilisation of human egg by human sperm) containing genetic material provided by more than 2 persons, and use such embryos;
c) create human embryos using precursor cells from a human embryo or a human fetus, and use such embryos;

d) undertake research and training involving the fertilisation of a human egg, up to but not including the first mitotic division, outside the body of a woman for the purposes of research or training;

e) create hybrid embryos by the fertilisation of an animal egg by human sperm, and develop such embryos up to, but not including, the first mitotic division provided that the creation or use is for the purposes of testing sperm quality and will occur in an accredited ART centre; and

f) create hybrid embryos by introducing the nucleus of a human cell into an animal egg, and use of such embryos.

The basic normative change involved is that one may create human embryos or human-animal hybrid embryos by any of the ways currently envisioned provided that one intends that they are not implanted in a woman and they are destroyed before 14 days of development. This is a change from the current circumstance in which one is only permitted to create human embryos by fertilization of an unaltered ovum by unaltered sperm for the purpose of achieving pregnancy.

This is a significant change from the position that Senator Patterson adopted in 2002 during the debate on the current legislation when she said: "I believe strongly that it is wrong to create human embryos solely for research. It is not morally permissible to develop an embryo with the intent of truncating it at an early stage for the benefit of another human being."

Senator Patterson's view then was consistent with the majority of the members of the Parliament who took a similar view in voting for the current legislation. Obviously a question to be addressed is what may have changed in the four years since.

In this submission I address the matter of the Lockhart Review and its findings for it would seem that the latter is the reason given for the Bill.

Before doing so, I would like to address a definitional matter that may cause some confusion.

2. Definition of "Embryo"

Senator Paterson's Bill contains a new biological definition of the human embryo. In the explanatory memorandum, the definition has been attributed to the NHMRC. I would like to draw to the attention of the committee that the proposed biological definition has not been promulgated by the NHMRC but has only been made available as a discussion paper prepared by an NHMRC Working Party. As far as I am aware, the NHMRC has not altered the position taken on this matter in the *Ethical Guidelines on the Use of Assisted Reproductive Technology in Clinical Practice and Research* developed by the Australian Health Ethics Committee. The guidelines were issued at the 154th Session of the NHMRC in 2004. The Australian Health Ethics Committee has statutory responsibility for developing ethical guidelines for medical research. The new proposed biological definition of the embryo has not been developed in a way that is

consistent with the ethical guidelines. Its use in this way is thus premature and problematic for the existing guidelines.

The new definition is:

> **A human embryo is a discrete entity that has arisen from either:**
>
> **(a) the first mitotic division when fertilisation of a human oocyte by a human sperm is complete; or**
>
> **(b) any other process that initiates organised development of a biological entity with a human nuclear genome or altered human nuclear genome that has the potential to develop up to, or beyond, the stage at which the primitive streak appears;**
>
> **and has not yet reached eight weeks of development since the first mitotic division.**

There would seem to be three problems if one were to try to apply the proposed definition in conjunction with the ART Guidelines (or in the context of the current legislation or Senator Paterson's Bill):

i) Part (a) arbitrarily makes the beginning not when the first cell is formed, but at a point sixteen hours later when the first cell begins to divide to form two cells. The new entity exists when the first cell is formed by the fusion of the two cells. That happens when the contents of the sperm are released into the ovum and the second polar body is extruded. At that time the two gamete cells have become just one cell. The later process of mitosis that occurs in order to replicate that first cell happens in an already existing cell. The mitotic division is not the beginning of the new entity, but something that occurs in an entity which already has a completed human genome and which is already organised for further development. The effect would thus be to remove the embryo for the first sixteen hours of development from the scope of regulation, either ethical or legal.

ii) Part (b) would subvert one of the purposes of the guidelines which is to prohibit forming embryos for any other purpose than to achieve pregnancy. In particular the guidelines prohibit so-called "therapeutic cloning". In the context of the new Bill it would subvert the intent of the 14 day rule. The definition is open to the interpretation that an embryo that is never to be transferred to the uterus of a woman lacks the potential to form a primitive streak. The formation of a primitive streak depends on implantation. Thus the second part of the definition would allow an interpretation that a cloned embryo was only an embryo if it is to be implanted. Thus it would be permissible, using this definition, to form embryos by cloning, as long as they were not to be transferred into an environment where it would be possible for implantation to occur and development to the stage of the formation of a primitive streak. Those unimplanted, cloned embryos would then be completely

outside the regulatory framework established by the guidelines and by the proposed legislation

In Victoria we had the experience, while the 1984 Act operated (until 1997) that there was a difference between the two main IVF teams. While the team associated with Monash University reported many embryos in the laboratory that were not implanted, the team associated with the University of Melbourne reported none. The discrepancy came about because the latter did not consider an embryo to be an embryo until it had successfully implanted.

The proposed definition is open to the same interpretation in relation to cloned embryos. The second part of the definition at least needs a qualifier such as adding the words "if placed in a suitable environment" after the words "potential to develop".

iii) A second problem with part (b) is that it may be possible to deliberately alter the process of fertilisation such that the entity formed is so disabled that it cannot implant and develop to the stage at which a primitive streak forms. The definition invites creativity aimed at disabling embryos in their formation. It would be preferable that the point of distinction, (between mere cell proliferation and the formation of an embryo), be the capacity to gastrulate and form a blastocyst if maintained in a suitable environment, rather than the capacity to form a primitive streak.

3. The Lockhart Review and Stem Cells

a) Confusion in the Debate

The ethics debate over stem cells is confused by the focus on cloning. There has been a distinct lack of clarity about the possible medical uses of stem cells and the ethical issues involved.

For those engaged in seeking solutions, the political contributions to the debate have been most unhelpful. When politicians and politicised scientists make claims about treating diseases such as Alzheimer's or Motor Neurone Disease by stem cell transplant from embryos formed by somatic cell nuclear transfer (SCNT), the groans from those engaged in neurological research are loud but largely unreported and politically unnoticed.

In scientific circles where I have an involvement, it is often said that it is not practicable to explain to politicians that the possible benefits from stem cells is not quite as direct as publicly imagined. Thus the public emphasis is placed on cultured stem cell transplant when this is becoming less and less the likely course as more is known about the difficulties of culturing stem cells and controlling their proliferation, differentiation and product.

The problem with this debate is that it has been oversimplified. Political supporters of cloning see miracle cures in embryonic stem cell transplant without being aware that this is not the major area of scientific interest in stem cells or a very likely source of cures. Opponents also tend to focus ethical concern only on the use of embryos.

b) What is likely?

For the record, it is worth noting that stem cell research is enormously interesting and promising, but not really because of the possibilities that human cloning might offer something new in that respect. The range of possible medical uses of stem cells would seem to include:

- Studies of disease process at a cellular level, possibly leading to cellular therapies
- Studies on the effects of drugs, toxicology, etc., on proliferating stem cells (rapid research results possible given rapid proliferation in culture, implications for determining currently unknown safety of drugs in early pregnancy)
- Stimulating activity in dormant stem cells in tissue (most promising new area without many of the ethical problems)
- Autologous transplant (e.g. bone marrow stem cells from the patient induced to develop as neurones may produce dopamine within the brain after transplant and thus partially treat Parkinson's Disease)
- Heterologous transplant (e.g. bone marrow transplants for Leukaemia is a well established practice)
- Transplant of embryonic stem cells from embryos post autologous Somatic Cell Nuclear Transfer (so-called "cloning" thought to be useful because if the embryo is formed from a somatic cell taken from the patient, then the stem cells will be histocompatible))

The defining characteristic of a stem cell is that it is pluripotent or multipotent because it is still at a progenitor stage of differentiation. *Pluripotent* means being able to form all cell types. *Multipotent* means being able to form a variety of cell types. *Totipotent* means being able to develop as an embryo. Stem cells exist in most, if not all, parts of the body.

c) Ethics and Stem cells

From an ethical perspective, the major issue about stem cells is that they have the capacity for enormous benefit if their growth and differentiation can be controlled, but they also have significant capacity for harm if that growth and differentiation is not controlled and they then cause disease. The latter is probably the major ethical issue in relation to the use of stem cells as a therapy.

One of the frustrating aspects of attempting stem cell transplant experiments is that after having controlled their differentiation to form the cell of the desired type, after transplant they just do not seem to perform well in terms of either producing the desired cell products or forming the desired tissue structures. This problem may ultimately defeat attempts to achieve new therapies by manipulating the differentiation of stem cells.

For this reason, thinking tends to be shifting towards stimulating activity in the dormant stem cells that are already in situ. Those cells are already of the right progenitor cell type. They are, of course histocompatible, being the patient's own cells. They require no culturing and thus none of the problems associated with cell cultures. It appears when

stimulated they are likely to develop cells of the right type with the desired cell products and capacity to form the right structures. They still may have the same problems, once having been stimulated, of possibly developing uncontrollably and thus causing disease. Safety is again the major ethical issue.

For practical purposes, stem cells may be classified into three categories:

- **Somatic** (non-embryonic, including adult, foetal, placental, umbilical cord). Somatic stem cells may be at various stages of progenitor cell and thus may be pluripotent or multipotent.
- **Embryonic** (harvested at end of first week after formation of blastocyst but before differentiation. Embryonic stem cells are considered pluripotent
- **Derived from gametes or gamete progenitors.** These stem cells are haploid and thus retain reproductive capacity (able to be used to from an embryo and thus raise the same ART ethical issues as using gametes).

So far little has been achieved to make embryonic stem cells controllable. There have been some stunning successes with adult cells, and the technology, such as bone marrow transplant, is well established. But little success even with adult stem cells in culturing a stem cell of one progenitor type to form cells of a different type and then function normally as the latter. However, embryonic stem cells remain scientifically interesting because more challenging and because they proliferate so quickly.

d) SCNT Embryonic Stem Cells

Embryonic stem cells developed by "cloning" individuals who have genetic disease are also interesting because the rapid proliferation of the cells produces more rapidly observable results to attempts to alter the progress of the disease process within the cells. The use of human SCNT embryonic stem cells to study Motor Neurone Disease is one such area that is being pursued by the scientists who developed Dolly the sheep. The embryos are formed by SCNT from an MND patient. But contrary to media reports, the goal is not ES cell transplant, but rather the development of drug therapies based on ES cell experiments.

A disadvantage of SCNT embryos is that they are epigenetically compromised. That is to say, because they have been formed using the nucleus of a somatic cell, many of the gene functions that would normally be available in an embryo are not available. The latter explains the problems of immune system diseases in cloned animals such as Dolly the sheep. (Dolly was euthanased.) It may also explain why it has proved to be so difficult to clone some animals, including humans.

SCNT embryos are also aged in the same way that somatic stem cells are aged, having shortened telomeres (the genetic factor related to ageing). They have not gone through the normal process of rejuvenation that occurs in the meiotic formation of a germ cell prior to the formation of an embryo by fertilization. The epigenetic and ageing problems, resulting from bypassing gametogenesis and fertilization, are likely to be persistent disadvantages for SCNT embryos.

In these respects, embryos produced in IVF by causing a fertilization process between gametes are superior to embryos produced by SCNT. Thus the untransferred embryos left in frozen-dried storage on IVF programs, when couples no longer want them, may offer more for stem cell research purposes than embryos manufactured by SCNT. These embryos are currently available for research approved by the Licensing Authority established under the legislation.

The SCNT embryos also involve the problem of obtaining ova and it is unlikely that women would be volunteering themselves for surgical harvesting of ova. It was this problem that seemed to trigger the events that exposed fraud at the Seoul University human cloning program. They were apparently obtaining human ova for their cloning experiments from young women research staff. That would be considered unethical in Australia and other developed countries. An American researcher working with the Seoul team blew the whistle.

The lack of available human ova, has also led to some teams experimenting with human SCNT to an enucleated animal ovum. Porcine and bovine ova have been used for this purpose. The practice is unlawful in Australia, but has been recommended by the Lockhart review and would be made lawful by Senator Patterson's Bill. The ethical problem is that it involves crossing a cultural and moral barrier between human and animal reproduction. There is no evidence of community support for forming human animal hybrid embryos.

e) Producing Embryos in Order to Destroy Them

The Senate debate is likely to focus on the issue of creating human embryos by SCNT, culturing them until a blastocyst forms when they are about a week old, and then harvesting the stem cells for research purposes. Predictably there will be a polarisation of views in the Parliament that reflects the polarity in the community.

It is worth noting that the National Health and Medical Research Council position on this issue in the past has been to allow excess IVF embryos to be used, but not to support creating human embryos for research purposes. The NHMRC has not changed that position which was originally expressed in the 1998 report *Scientific, Ethical and Regulatory Considerations Relevant to Cloning of Human Beings* and repeated in the 2004 *Ethical Guidelines on the Use of Assisted Reproductive Technology in Clinical Practice and Research.* This was also the position of compromise adopted by the Parliamentary enquiries and by the Commonwealth.

Nothing has changed scientifically to support some kind of new argument of necessity to use SCNT embryonic stem cells. If anything, the possibility of developing therapies involving cultured embryonic stem cell transplant has become more remote as more has become known about the difficulties.

f) Lockhart – No Proof of Concept

One unfortunate aspect of the polarity on the status of the embryo is that it tends to obscure other issues and the actual nature of the research. In the future, there may be some greater benefit to be obtained from using embryos, but as a matter of science it is not clear that they will be of benefit. There seems to be little reason to overturn the existing compromise supported last time by the NHMRC and by a large majority in the Parliaments. A balanced approach may be to maintain the status quo allowing access to excess IVF embryos only and then address the question of deliberately creating them for research purposes at some time if the future if and when animal models show some evidence that benefit is to be obtained from them.

The Lockhart report showed no strong reason for allowing the creation of embryos for research purposes. Lockhart was in fact a very odd piece of reporting. One of the oddities was recommendation twelve in which the committee recommended, "Creation of human embryos by fertilization of human eggs by human sperm should remain restricted to ART treatment for the purposes of reproduction". That is an instance of the extraordinarily blinkered vision that characterizes the report. The recommendation would prohibit natural fertilisation. There would not seem to be community support for that!

In fact much of the report seemed to be based on scientific adventurism rather than on established scientific fact or what would be acceptable to the community. Lockhart supports formation of human-animal hybrid embryos, either by fertilisation between human and animal gametes or by human SCNT to an animal ovum. The committee also supported forming embryos by SCNT using genetic material from more than one person.

The failure to address whether there was an established necessity to create human embryos for research purposes was an instance of a failure to address the facts. In fact the animal studies so far have not established proof of concept for stem cell therapies derived from SCNT embryos. Lockhart served only to inflate the hype that so frustrates responsible scientists seeking to develop cellular therapies. Few actually want any involvement with creating embryos for this purpose.

The Lockhart enquiry shows the error in appointing a committee of people on the basis that they supported a technology, rather than on the basis of representing community interests. It was an odd committee, a creature of the Council of Australian Government (COAG) in which each of the state Premiers and the Prime Minister were able to nominate candidates, and no-one applied criteria for balance and representation of either expertise or community interests in the overall composition.

4. Different Models of Regulation

I have never been a supporter of using legislation, such as the current cloning and embryo legislation, to regulate medical research. It is my view that the blunt instrument of the law which defines offences and establishes penalties and for which the rules of evidence and prosecutorial processes would apply, is not the preferred method of regulating

medical research in areas in which terms and concepts are continually changing. Such laws are basically unenforceable and they make regulation clumsy.

It is, in my view, quite inappropriate for scientists acting in good faith to be anxious about the heavy hand of the law descending. It is also inappropriate to create offences in these areas that would require the intervention of police officers to implement them.

Agencies that receive Commonwealth Government research funding are already regulated by their deeds of agreement with the Commonwealth in which they commit to abiding by the NHMRC National Statement and other ethical guidelines for human research such as the ART guidelines. It would be simple enough matter to legislate to require similar compliance by corporations funding or engaging in human research.

The National Statement relies upon a system of institutional Human Research Ethics Committees. The latter system has the capacity that the law does not have to adapt to scientific developments.

One of the oddities that would occur if Senator Paterson's Bill became law would be that private bodies could do all that the Bill makes lawful, but Commonwealth funded bodies, such as the Australian Stem Cell Centre and the universities would be prohibited by their deeds of agreement and the NHMRC guidelines from undertaking those procedures.

Usually ethical developments precede the law. In this case, Senator Patterson's Bill precedes any such development within the NHMRC and the Australian Health Ethics Committee. The Lockhart review was not an ethical review. It lacked the community representativeness that the Australian composition contains. It is puzzling that the Parliament should be pursuing new proposals for medical research that have been rejected previously by the Australian Health Ethics Committee as the peak medical research ethics body in the country, are currently the subject of ethical prohibitions, and which have not been the subject of a more recent reference to AHEC.

Yours sincerely,

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