SUBMISSION TO THE SENATE COMMUNITY AFFAIRS COMMITTEE INQUIRY

INTO

THE SOMATIC CELL NUCLEAR TRANSFER (SCNT) AND RELATED RESEARCH

AMENDMENT BILL 2006

AND

THE PROHIBITION OF HUMAN CLONING FOR REPRODUCTION AND THE

REGULATION OF HUMAN EMBRYO RESEARCH AMENDMENT BILL 2006.

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Men always learn from their mistakes how to make new ones (1)
(Gender restriction not implied).

1). This submission presents my personal response to the two Bills which are the subject of inquiry. It does not purport to represent the views of any other person or of any group, government or non-government, with which I am associated.

2). The primary concern that I wish to outline in this submission is that both Bills contain serious flaws which will impede effective regulation of the research to which they refer. I propose to consider the two Bills in the order in which they have been presented to the Senate with the qualification that, when the issues raised are similar in both, they will be considered in my response to the first Bill. I believe that the likelihood of subsequent successful implementation of any legislation will be inversely proportional to the speed with which the two Bills are considered by the Parliament. While there has been much discussion of the speed of changes occurring in stem cell science, the magnitude of the recision of cautions which have been retained in successive versions of ART guidelines that is envisaged in these Bills can only be described as a regime change. If the Bills are implemented in their entirety, the legislators will not just have overtaken, but will be far ahead of the scientists.

3). The **definition** of a human embryo is dealt with in Schedule 1, para 1. It is common for proposals dealing with embryo experimentation to launch new definitions of 'embryo' to meet its requirements and this Bill does not disappoint. The selected definition is derived from a discussion paper, *'Human Embryo' – A Biological Definition*, released by the NHMRC in December, 2005. This paper presents considerable background information on the subject of embryological nomenclature with the intention, expressed in its Preface, of eliciting comment from a 'wider audience'. The incorporation of its

definition in legislation in the apparent absence of any widespread debate to inform the Parliament of community attitudes on its specific features could be regarded as inappropriate. The choice of words by the draughtsperson responsible for the Explanatory Memorandum accompanying Senator Patterson's Bill verges on the Freudian: *It is intended that paragraph (b) of the NHMRC definition would capture the following types of embryo* (Item 3).

4). I wish to comment on some aspects of the Discussion Paper and then on its use in the Bill. The Paper emphasises that it is intended to confine its consideration to **biological** aspects of definition and I intend to do likewise (specifically excluding philosophical considerations) while recognising that there are **semantic** issues which are inextricably intertwined with the biological. When the definition is transposed from a scientific discussion paper to a legislative document, subsequent interpretation of biological questions will necessarily be confined by the semantics selected.

5). Some background to the **history** of the embryo-related vocabulary generated since the advent of IVF, with which Committee members may not be familiar, will help to indicate why I regard semantic aspects of the definition under discussion as very important. As an example, the Discussion Paper refers to a paper by a British embryologist, Anne McLaren *(2)* to the effect that: *the practice of using the term 'embryo' for the entire product of the fertilised egg, most of which differentiates before the formation of the primitive streak into tissues that will protect and nourish the future embryo, has led to much confusion in the general community*. It is interesting, however, to recall that McLaren, a member of the Warnock Committee, wrote specifically in response to criticism of her role in popularising the term 'pre-embryo' as a means of setting a cut off time before which no embryo existed. The criticism to which McLaren replied, from David Davies, quondam editor of *Nature*, was: *I cannot claim to have read every word submitted to the Warnock Committee of Inquiry into Human Fertilisation and Embryology of which I was a member, but am reasonably sure that at least in our discussions the word 'pre-embryo' was never used (3).* Davies proceeded to deplore the use of 'cosmetic words'.

6). In canvassing possible definitions, the Discussion Paper comments that: *Given this ongoing dilemma it might be counterproductive to develop yet another definition of 'human embryo' that relies solely on a specific developmental time point to pinpoint the demarcation between 'embryo' and 'not-embryo'*. The basic biological point that requires emphasis is that the placement in time of any developmental point is entirely at the mercy of the technology which is available at the time to **recognise** when that point has been attained. Inevitably, the time of recognition will move closer to the actual time of occurrence of the event as science advances. In general terms, if one is basing detection on morphological grounds using microscopy alone, its timing may become earlier as resolution of the microscope improves. When a biochemical recognition assay is developed, the timing of recognition may approach that of the actual biological event much more closely. The approximation will become even better as the sensitivity of the biochemical assay improves so that it becomes practicable to detect fewer molecules indicative of the event. The Discussion Paper acknowledges the divergence between the

occurrence and its recognition in 2.3 in pointing out that: ***syngamy can not be visually confirmed on a live entity until the first mitotic division is initiated.***

7). Are all available markers of developmental time points usually considered in attempts to adjudicate on whether biological events with possible philosophical or semantic implications have occurred? No. A very well documented biological phenomenon which appears never to get a guernsey in discussion of 'marker events' in embryological development is the release of **Early Pregnancy Factor (EPF)** as an indication of the existence of a discrete new entity. This molecule was first discovered by a Queensland scientist, Halle Morton, 3 decades ago. Since then it has been extensively researched both in Australia and internationally. This has been reviewed by Morton *(4).* Early pregnancy factor was first detected in mice but has since been demonstrated in many species, including us. Its great scientific interest is that it represents the means by which a single cell organism communicates with a trillion cell one. This entails amplification of the message (***I'm here***) by a 'cascade' mechanism with resemblance to that responsible for blood coagulation. EPF is produced at the single cell stage of development and Morton has demonstrated its appearance within 6-24 hours of a fertile mating. I suggest that it is a much more sensitive indication of the appearance of a new entity (historically referred to as an embryo) than any other. It certainly represents a recognition signal which is observable much closer to the event it signifies than any other. The legitimacy of EPF as a marker of the generation of a new entity is that its detection in, but subsequent disappearance from, maternal serum, **is accepted by obstetric researchers as the basis for postulating a high normal incidence of pregnancy loss** following traditional breeding strategies. It could easily be argued to have a better biological basis than more arbitrarily defined 'markers'. The arbitrarily selected 14 day 'marker' is a prime example of the way in which opinion can be given biological flesh in legislation (I think that the most eloquent exposure of the '14 day rule' is the individuation explanation given by Mary Warnock to an Australian newspaper: *It was chosen because it was when I became me.)*

8). I submit that if a consensus decides that the entity produced by either of the precedent processes specified in the proposed definition should, under licence, be available for research it would be more honest and transparent to legislate that certain **embryos** up to a specified age may be so used. This would also be semantically preferable in that it would avoid the cosmetic devices referred to above by Davies.

9). The Explanatory Memorandum attached to the Bill appears to have failed to grasp the meaning of part (b) of the proposed definition and, given that the Memorandum might be used as a source of information to clarify ambiguity in the Bill if this is enacted, this should be a cause of concern to the Committee. In the definition as included in schedule 1 at para. 1 , the reference to the appearance of the primitive streak identifies the **potential** to develop to this stage (subsequently) as a defining attribute of 'embryo-ness' at an earlier time. However, the Explanatory memorandum completely misses the bus and concludes, in relation to the definition used in the Bill, that: *This definition allows medical science more options in research involving embryos, but it maintains the*

limitation in the original Act that the embryo must have gone no more than 14 days development. It does nothing of the sort.

10). Para 14 , (4) states: *A person commits an offence if the person intentionally places a non-ART embryo in the body of a woman for any purpose other than achieving pregnancy.* This sentence raises several questions which I will raise in the sequence in which they arise. How is it envisaged that one would go about **unintentionally** placing an embryo? As breaches of the enacted Bill are to attract criminal sanctions, it would be interesting to hear how the draughtsperson considers that a potential defence of unintentionality would be mounted. The phrase 'non-ART embryo' is not defined in the Bill. What is it intended to designate? Presumably, a 'free range' embryo produced by traditional means (and illegally flushed from the uterus) would fall within this category? What other categories of 'non-ART embryo' are envisaged in 14 (4)?

11). Para 21 (3) (c) deals with the production of human/non-human hybrids. There is a significant omission. It is mildly paradoxical that the avoidance of animal use has often been advanced as a reason for experimenting with IVF embryos, whereas this proposal, lf accepted, will reintroduce animal use. One consequence of such a decision will be to mandate the consideration and approval of each proposal for producing hybrids by an Animal Experimentation Ethics Committee duly constituted in accord with the relevant NHMRC regulations. Animal Experimentation Ethics Committees are charged with determining that the proposed research is novel and worthwhile and that the numbers of animals that it is proposed to use will be adequate, but will not exceed, the number required to achieve a statistically significant result. Committees also operate with the goals of replacement, reduction and refinement of animal usage which, with respect, I would commend to the Community Affairs Committee.

12). Senator Patterson's Bill contains more specific detail about the use of animal-human hybrids and the following comments are based on it and its accompanying Explanatory Memorandum. The two specific protocols which the Bill sanctions, under licence, are the fertilisation of animal eggs by human sperm as a means of testing the chromosomal complement of the sperm and the introduction of the nucleus from a human cell into an enucleate animal egg. They will be considered separately.

13). The introduction to the Explanatory Memorandum accompanying Senator Patterson's Bill spells out, quite explicitly, the dependence of the Bill on the recommendations of the 2005 Legislative Review (a.k.a. Lockhart) Committee. In relation to the testing of human sperm by allowing them to fertilise non-human oocytes, the report of that Committee states (in para 4.3 concerned with "Effect of Legislation on Research") that: *The prohibition of creation of human-animal hybrid embryos (PHC Act s20), combined with the current definition of an embryo has also prevented other research or testing requiring fertilisation (such as tests for sperm quality by fertilisation of hamster eggs).* Hamster eggs are especially suitable for use in this assay, originally developed by Susumu Ohno. Apparently, notwithstanding their collective expertise in a variety of fields, no member of the Legislative Review Committee was aware that the importation or breeding of hamsters in Australia has been illegal for most of the last

century. Puzzled by the above conclusion in the Committee's report, I contacted the Australian Quarantine and inspection Service (AQIS) this afternoon (3/10/06) requesting information on permissions given for importation of hamsters for medical research.. While confidentiality considerations precluded release of numbers, I was informed that such importation in the past decade has been restricted to castrated male animals (it would require scientific brilliance exceeding even that needed for SCNT to generate hamster oocytes from these immigrants). Perhaps some other species was used by the practitioners who testified to the Legislative Review Committee about the inhibitory effect of the PHC Act on their activities (if this were not the case, both I and AQIS would be keen to know more). However, even if identification of the incorrect species to the Committee was just a simple error (or a terminological inexactitude), it reinforces the concern already expressed in (4) above, namely that the science is at the mercy of semantics once it falls into the clutches of the draughtsperson.

14). The other protocol which 'Lockhart', and Senator Patterson's Bill sanctions is the placement of a human cell nucleus in an enucleate animal oocyte. This procedure has been used in a few acknowledged instances overseas. In the most notorious of these, Advanced Cell Technology, Worcester produced a human-cow hybrid which was allowed to develop for several days. When this experiment became known, some time later, it evoked considerable disgust from the U.S. community, including condemnation from President Clinton, hardly an opponent of embryonic stem cell research. The reason given for sanctioning this protocol in Senator Patterson's Bill is that of circumventing the requirement for large numbers of human oocytes (I shall return to this below). The uses envisaged for these hybrid embryos are three – research, training and clinical application. Each of these merits consideration. The thorough development, in animal models prior to human testing, of any procedure with potential for human therapeutic application was a *sine qua non* of medical research before the availability of large collections of IVF human embryos led to short-circuiting of the practice of an exhaustive 'work up' in animals before the introduction of human testing. Proposals for encouraging testing in animal systems, such as the establishment of a non-human primate colony (which I presented as a member of the working party responsible for the 1998 advice to Minister Wooldridge) were heavily disparaged by researchers in the field. Yet, studies within one (non-human) species would be much more likely to provide *interpretable* data than those obtained in highly contrived inter-species hybrid experiments.

15). The second reason advanced by 'Lockhart', and supported by the proposed legislation, for producing hybrid embryos was given as 'training'. I quote from the foreword to a manual on embryological techniques written by an expatriate Australian, Wes Whitten, who worked for many years at the Jackson laboratory. I suggest, with respect, that Whitten's contribution to embryology will be assessed ultimately as greater than that of any contemporary Australian researcher. He wrote: *I declined to become involved in the development of media for human ART because I could not see any way of ethically obtaining sufficient numbers of ova to carry out significant experiments and because more interesting basic research could be carried out with mice for which I was ideally situated. Fortunately, mouse embryos proved to be useful models for human ART*

and they are still being used for teaching ART, for developing new techniques and for quality control of media, equipment and techniques (5).

16). The third reason proposed for production of hybrid embryos was described as 'clinical application'. This presumably refers to **human** clinical use. This appears to be drawing an even longer bow than its two precursors. It should be recalled that a compelling justification advanced in 2002 for permitting production of additional embryonic stem cell lines was that all lines existing at that time had been exposed to 'feeder layers' of mouse fibroblasts. The risk of contamination was said then to be such that the US FDA would not approve clinical application of these cell lines. **That risk** fades into near insignificance compared with the risk of therapy with cells partially derived from animals. Refer to the current NHMRC advice on xenotransplantation.

17). The two Bills are interesting not only for what they contain but for what they discretely ignore. As mentioned above by Whitten, the problems involved in harvesting adequate numbers of oocytes from donor women were substantial. With the proliferation of new ideas, 'supply side' issues have become much more substantial. The Bills and their accompanying memoranda have chosen to ignore them. I will leave consideration of them to Committee members while drawing attention to the approval given recently to a group at Durham university in the UK to offer substantial financial inducements to women to provide oocytes for use in SCNT research .

18). In dealing with the possibility of using embryos deemed unsuitable for placement in the uterus because of adverse PGD findings or poor morphology (described in 'Lockhart' and in both Bills as unsuitable for 'implantation' – an embryo implants **itself** - a technician can place it in the uterus but can't implant it), Senator Patterson's Bill identifies the requirement for a 'cooling off' period, after consent to use but before use begins, as an impediment. It is of interest to revisit the Senate Community Affairs Committee report prior to the 2002 Acts. Para 4.64 reads: *Another suggestion was Stem Cell Sciences' proposal that a 'cooling-off' period be imposed to ensure that potential donors have the opportunity to fully consider whether they wish to authorise the exempt use of their embryos.* The NHMRC Guidelines on ART specify a substantial period – 14 days – for this. The Explanatory Memorandum canvasses the possibility of having an 'early release' involving a truncated cooling off period for 'unsuitable for implantation' embryos so that they can be used for research. The alternative path of declaring them to be 'excess to requirements' is not favoured in the memorandum. It is pointed out by 'Lockhart' that existing Victorian legislation would preclude such a declaration. I disagree with this recommendation on the basis that to tamper with the general recommendation for an adequate 'cooling off' period in order to overcome one specific difficulty is a bad approach (the 'What never – well, hardly ever' solution). If the Senate believes that these 'unsuitable for implantation' embryos could advance research, it is preferable to arrange its legislation so that they **may** legitimately be declared as 'excess' so permitting their cryopreservation followed by incorporation of the regular incorporation of an appropriate 'cooling off' period before use.

19). I am willing to answer any questions which the Committee may have on the matters raised in this submission.

Peter McCullagh,

References.

1. Taylor, AJP (1954) in *The Struggle for Mastery in Europe.* Taylor referred to the Austrian Government's failure to learn from the experience of the Crimean War when it sought to initiate war with Sardinia 4 years later.
2. McLaren, A (1986) Embryo research. *Nature, 320,* 570.
3. Davies, D (1986) Embryo research. *Nature, 320,* 208.
4. Morton, H (1998) Early pregnancy factor. *Immunology and Cell Biology, 76,* 483-496.
5. Ali, J (2003) *A Practical Guide to Mouse Preimplantation Embryology and human Assisted Reproduction Technology.*