ON HUMAN CLONING

A Position Statement

Australian Academy of Science

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Contents

Executive summary

We define ***cloning*** as *production of a cell or organism with the same nuclear genome as another cell or organism.* We have chosen this simple definition to reduce ambiguity in public discussion, to guard against legislative misinterpretation and to underpin any regulatory or licensing guidelines. In this Statement we distinguish between *reproductive cloning* to produce a human fetus and *therapeutic cloning* to produce human stem cells, tissues and organs.

It had been widely accepted that cell differentiation (or increasing cell specialisation) in the developing mammal is irreversible, until the recent successful *reproductive cloning* of sheep, cattle and mice from adult cells. These experiments suggest that it may also be possible to reprogram human adult cells to revert to earlier stages of development. Speculation in the popular press about selfish or compassionate reproductive cloning of humans has tended to obscure the real scientific challenges in capturing this advance in knowledge for *therapeutic cloning*, for the benefit of mankind.

Cloning techniques may one day revolutionise medical treatment of damaged tissues and organs, should it become possible to use human adult cells as the starting material for growth of new tissues. At present, one human organ, skin, can be grown in the laboratory to provide self-compatible skin grafts for burns victims. The possibility of growing other self-compatible cells, such as nerve cells for patients with spinal injuries or muscle cells for heart attack victims, could one day be a reality, albeit within an unknown timeframe. That such a possibility could become a reality is suggested by the combined application of knowledge arising from three recent and significant advances in biomedical research.

These advances are (a) the cloning of mammals from adult cells; (b) the establishment of cultures of 'all-purpose' cells, human embryonic stem (ES) cells with the potential to grow into many different cell types; and (c) the demonstration that human fetal nerve stem cells can develop into multiple and appropriate nerve cell types following

transplantation (into experimental animals). These findings provide new opportunities for research in cellular and developmental biology and, taken together, suggest that future possibilities may exist for self-compatible tissue and organ repair.

The Council, in accord with international opinion, considers that reproductive cloning to produce human fetuses is unethical and unsafe and should be prohibited. However, human cells, whether derived from cloning techniques, from ES cell lines, or from primordial germ (reproductive) cells should not be precluded from use in approved research activities in cellular and developmental biology.

In Australia at present, production of human ES cells would be approved only in exceptional circumstances under National Health and Medical Research Council (NHMRC) *Ethical guidelines*, originally prepared to ensure ethical practices in *in vitro* fertilisation (IVF) clinics. For Australia to participate fully and capture benefits from recent progress in cloning research, it is necessary to revise the 1996 NHMRC *Ethical Guidelines on Assisted Reproductive Technology* and repeal restrictive legislation in some States. This could be done in the context of establishing a national regulatory arrangement, taking into account recent advances in biomedical research and advocated best practice elsewhere. The regulations should be binding on both publicly and privately-funded research activities.

Noting that the Australian Health Ethics Committee (AHEC) has recommended (December, 1998) that *the Minister for Health and Aged Care should urge States and Territories to introduce legislation to limit research on human embryos according to the principles set out in the NHMRC Ethical Guidelines on assisted reproductive technology*, the Council of the Australian Academy of Science makes the following **recommendations** with respect to existing and any proposed regulatory and legislative arrangements regarding human reproductive and therapeutic cloning.

Recommendations

1. Council considers that reproductive cloning to produce human fetuses is unethical and unsafe and should be prohibited. However, human cells, whether derived from cloning techniques, from ES cell lines, or from primordial germ cells should not be precluded from use in approved research activities in cellular and developmental biology.
2. Council strongly supports the recommendation of the Australian Health Ethics Committee that the *Minister for Health and Aged Care should encourage and promote informed community discussion on the potential therapeutic benefits and possible risks of the development of cloning techniques.*
3. If Australia is to capitalise on its undoubted strength in medical research, it is important that research on human therapeutic cloning is not inhibited by withholding federal research funds or prevented by unduly restrictive legislation in some States.
4. It is essential to maintain peer review and public scrutiny of all research involving human embryos and human ES cell lines undertaken in Australia. Council supports the view that a national regulatory two-tier approval process be adopted. Approval to undertake any research involving human embryos and human ES cell lines would need to be obtained from a duly-constituted institutional ethics committee (IEC) prior to assessment by a national panel of experts, established by the National Health and Medical Research Council, on the scientific merits, safety issues and ethical acceptability of the work.

Introduction

The great public and scientific interest, the potential ethical issues and the therapeutic benefits which may arise from applications of cloning techniques have led the Australian Academy of Science to develop this position Statement on human cloning. This Statement has been developed in 1998 for the Council of the Academy by a Steering Group comprising Professor John White (Chair), Dr Oliver Mayo, Professors Philip Pettit and Roger Short and consultant Professor Sue Serjeantson. A group (Annex 1) representing scientists, lawyers, philosophers, religious bodies and the Commonwealth regulatory authority was consulted in a one-day Forum to identify wider issues arising from the foreseen scientific challenges and therapeutic possibilities.

This paper examines scientific advances since the cloning of the sheep "Dolly" in 1997 and their implications.

Three scientific developments, taken together, suggest new opportunities for research in tissue and organ repair.

These advances are

- the cloning of mammals from adult cells;
- the establishment of cultures of 'all-purpose' cells, human embryonic stem (ES) cells with the potential to grow into many different cell types; and
- the demonstration that human fetal nerve stem cells can develop into multiple and appropriate nerve cell types following transplantation (into experimental animals).

These findings provide new opportunities for research in cellular and developmental biology and, taken together, suggest that future possibilities may exist for self-compatible tissue and organ repair in humans.

A definition of Cloning

We define ***cloning*** as *production of a cell or organism with the same nuclear genome as another cell or organism*. We have chosen this simple definition to reduce ambiguity in public discussion, to guard against legislative misinterpretation and to underpin any regulatory or licensing guidelines.

The word *clon* (from the Greek *klon*), a twig or cutting, was used by Herbert Webber[1] to describe plants that are

propagated vegetatively. The term (later, *clone*) was adapted to cell culture by biologists, including by Sir Frank Macfarlane Burnet in 1958 in his book *The Clonal Selection Theory of Acquired Immunity*. More recently, the term *clone* has been used to describe animals that share a nuclear genome.

Reproductive cloning to produce a human fetus by nuclear replacement is unethical and unsafe.

Therapeutic cloning to produce human stem cells, tissues and organs is a separate issue.

In this Statement we distinguish between *reproductive cloning* to produce a human fetus by nuclear replacement and *therapeutic cloning* to produce human stem cells, tissues and organs. Cloning of human cells and of human DNA (genes) are routine procedures in many laboratories, as is the cloning of human skin, and will not be discussed here. Also, we shall not discuss here embryo-splitting, sometimes called *twinning*, the natural form of cloning that can lead to two or more identical fetuses.

Scientific implications of cloning

The cloning of 'Dolly' the sheep has important scientific and ethical implications.

The cloning of 'Dolly' the sheep from the nucleus of an adult somatic cell in 1997[2] was the first example of production of viable offspring by transfer of a cell nucleus from an **adult** mammal into an unfertilised, enucleated egg. This was not the first time a sheep had been produced by nuclear replacement. In 1996, two genetically identical sheep were cloned by nuclear replacement using cells from nine-day embryos as the nuclear donors[3]. This earlier report did not create alarm or much surprise; indeed, Willadsen[4] had shown a decade earlier that viable offspring could be produced by fusion of enucleated eggs from sheep with separated eight-cell stage blastomeres (any one of the cells into which the fertilised ovum divides). 'Dolly' was different from earlier clones because she was derived from an adult mammary gland cell. This experiment, now replicated in an experimental mouse model[5] and in cattle[6], has important scientific and ethical implications which include:

- the potential for better understanding the process of cell differentiation and its reversal, and of ageing;

- the potential to modify genes of domestic livestock in more efficient ways; and
- the possibility of therapeutic cloning of human tissues or reproductive cloning to produce human fetuses.

Understanding the process of cell differentiation and its reversal, and of ageing

While it has been widely accepted that cell differentiation is unidirectional and irreversible, Rossant[7] in reviewing the history of nuclear replacement experiments in amphibia and in mammals, concluded otherwise. The classic experiments by Briggs and King[8] in a frog *Rana pipiens*, and by Gurdon[9] in another frog *Xenopus laevis*, provided evidence that the genetic content of differentiated somatic cells is essentially unchanged from that of the early embryo. Gurdon transferred nuclei from adult skin cells to produce fully developed tadpoles, but no viable adult frog was produced from an adult differentiated nucleus. This was attributed to chromosomal damage during the process of nuclear replacement, but left open the possibility that there was some genetic loss in the differentiated adult cell.

It should be possible to reprogram almost any cell to grow into a different cell type.

Recent advances in molecular biology have increased our understanding of the regulation of gene expression, which is maintained by continuously active control mechanisms[10] in which regulatory proteins bind to DNA sequences adjacent to genes, to turn them on or off. Gene expression can also be modified by inherited methylation, known as parental genomic imprinting[11]. Rossant concluded that it should be possible to reprogram almost any adult cell to initiate earlier programs of differentiation.

Cloning techniques provide particular opportunities to answer important questions about ageing. Is the cloned sheep, 'Dolly', biologically as old as her mother despite the chronological difference in their ages? Does 'Dolly' have shortened telomeres (tips of chromosomes, which shorten at each cell division) or were these repaired in the host (telomerase-rich) oocyte environment? Does 'Dolly' have an accumulated mutational load that reduces life-span and increases risks for cancer and other diseases?

Cloning in domestic livestock may be used to produce human drugs and to improve livestock productivity.

The potential to modify genes of domestic livestock in more efficient ways

The prospect of large-scale cloning in domestic livestock may make more efficient the production of transgenic livestock, for the purposes of:

- improved livestock welfare or product safety;
- improved livestock productivity;
- production of biological pharmaceutical agents;
- production of organs or tissues for transplantation into humans; and
- development of animal models of human disease.

There may be particular safety concerns relating to some of these proposed purposes, such as the (unknown) capacity for porcine retroviruses to be transferred to the human population at large through xenotransplantation. There may be particular ethical concerns regarding the deliberate introduction of human-like disorders into experimental domestic livestock. In addition, there may be more general ethical and social concerns about human applications of knowledge gained from research in somatic nuclear replacement in livestock.

In the mouse, genetic modification of the germ-line to 'knock-out' particular genes or introduce new or altered genes has been facilitated by the availability of ES cells that continue to grow as undifferentiated stem cells when cultured *in vitro*. Development of transgenic mice is further facilitated by the short generation times that permit rapid production of mouse inbred lines that are homozygous for the gene (or lack of the gene) of interest. In the past, it had proved difficult to establish ES cell lines in domestic livestock, stimulating research interest in developing an alternative system, such as large-scale cloning, for genetic modification. Until recently[12], there has been a low success rate in generating transgenic domestic livestock using expensive *in vivo* techniques. The cloning technology makes it possible to use cheaper, *in vitro* protocols.

Reproductive cloning has a poor success rate.

Recent successes in sheep[13] and in cattle[14] in genetic engineering of fetal fibroblasts followed by fusion of cells to enucleated oocytes, suggest that efficient gene transfer systems may soon be available to livestock breeders without the need to resort to cloning from adult tissue. Further, early

reports of experimental sheep[15] and pig[16] ES cell lines are now emerging. Some observers believe that there is little commercial incentive to repeat the 'Dolly' experiment in domestic livestock, especially given the poor efficiency of the original technique; 'Dolly' was the only survivor of 277 cell fusions, including 29 transferred blastocysts. Increasingly more efficient gene transfer techniques in large animals may render the current cloning technology relevant for special purposes only; for example, for introduction of a single gene into an animal of known phenotype.

The poor success rate in the generation of cloned mammals does in itself raise important questions in basic research: what is the basis of the high pregnancy failure rate, for example? Is this related to failure to re-establish appropriate genomic imprinting or to chromosomal damage as in Gurdon's *Xenopus* clones or to a double-dose of mitochondrial genes.

The possibility of therapeutic cloning of human tissues or reproductive cloning to produce human fetuses

It is the possibility that technical barriers to the cloning of humans may have been overcome that stimulated the widespread interest in the cloning of 'Dolly'. The safety problems outlined above nevertheless remain. Speculation in the popular press about reproductive cloning of humans from individual adult cells has tended to obscure the real scientific challenges involved in capturing this advance in knowledge for the benefit of mankind. The failure rates in animal cloning are such an example. Future applications of therapeutic cloning are considered later in this Statement.

Speculation about reproductive cloning of humans has tended to obscure the scientific challenges in capturing therapeutic cloning technology for the benefit of mankind.

National and international responses to human cloning

The initial Australian Government response to advances in cloning techniques (Annex 2) came on January 14, 1998, when the Federal Minister for Health and (then) Family Services, Dr Michael Wooldridge, affirmed that the Australian Government agrees with the UNESCO *Declaration on the human genome and human rights*.

December 16, 1998 the Australian Health Ethics Committee (AHEC) of the National Health and Medical Research Council (NHMRC) provided the Minister with advice (Annex 2) on *Scientific, Ethical and Regulatory Considerations Relevant to Cloning of Human Beings*.

This advice does not adequately distinguish between undesirable reproductive cloning to produce human fetuses and desirable therapeutic cloning of human tissues and organs. It recommends that the Minister urge States and Territories to introduce legislation to limit research on embryos according to guidelines originally prepared to ensure ethical practices in *in vitro* fertilisation (IVF) and embryo transfer.

Although the 1996 NHMRC *Ethical guidelines* would seem to permit production of human ES cells in exceptional circumstances, AHEC advises that *production of embryonic stem cell lines is contravened* (sic) *by the Victorian and Western Australian Acts and NHMRC Ethical Guidelines* (AHEC advice on *Scientific, Ethical and Regulatory Considerations Relevant to Cloning of Human Beings*, para. 4.32).

This means that some of the important starting material for therapeutic cloning of human tissues and organs might continue to be prohibited from use in research in Australia if the AHEC recommendations were to be implemented. The current Australian regulatory and legislative framework of relevance to human cloning is summarised in Annex 3.

Other national responses to advances in cloning techniques appear to be less prohibitive (Annex 4). In the United Kingdom, government advisors have recognised that legislation introduced in 1990 to ensure ethical practices in research in IVF and embryology has been overtaken by advances in cloning techniques. In December, 1998, the UK Human Genetics Advisory Commission and the Human Fertilisation and Embryology Authority recommended that licences might be issued for research involving human embryos for development of therapeutic treatments for diseased or damaged tissue or organs.

In the United Kingdom, Government advisors recommend that licences might be issued for research involving human embryos for development of therapeutic treatments.

Also in the United Kingdom, the Human Fertilisation and Embryology Act of 1990 forbids the replacement in the uterus of any embryo used for research. In contrast, the Australian NHMRC 1996 *Ethical guidelines* state that *non-therapeutic research which involves the destruction of an embryo, or which may otherwise not leave it in an implantable condition, should only be approved by an institutional ethics committee (IEC) in exceptional circumstances.*

The Academy's Steering Group has studied the U.K. advice and its basis and believes it has many features worth adapting to the Australian research environment.

In the United States of America research using cloning techniques is essentially unregulated in private clinics but federal government funds, including funds from the National Institutes of Health (NIH), may not be used for any research involving embryos. NIH has stated (January, 1999) that it is legal for the agency to fund research using human ES cells grown by privately funded scientists (Annex 4).

Recommendation 1:

Council considers that reproductive cloning to produce human fetuses is unethical and unsafe and should be prohibited. This is in accord with international opinion (Annex 5). However human cells derived from cloning techniques, from ES cell lines, or from primordial germ cells should not be precluded from use in approved research activities in cellular and developmental biology.

Future therapeutic applications of cloning methods

Current practices in treatment of degenerative diseases may one day seem bizarre if the prospects for therapeutic cloning technologies are realised.

The potential for new therapeutic applications comes from the combination of advances in cloning techniques, in cellular and developmental biology and in genetic technologies. Cloning not only provides the prospect of replacement tissues and organs, but also provides a vehicle for delivery of gene therapy. Developments in these areas of research are likely to generate controversial issues in bioethics but may ultimately make many current medical practices seem crude, if not macabre.

Consider, for example, the former practice of extracting human growth hormone and gonadotrophins from the pituitaries of human cadavers, with the attendant risk for the recipient (as is now known) of developing Creutzfeldt-Jacob Disease[17]. This practice has been abandoned, following scientific advances that enabled production of unlimited quantities of pure hormones by genetically engineering bacteria. Similarly, the practice of harvesting insulin for diabetes patients from the pancreas of the pig, with attendant risks that the patient might develop anti-pig insulin antibodies, has now been overtaken by the provision of genetically engineered, pure human insulin.

Genetic engineering was not universally accepted in the early 1970s, on safety and ethical grounds, and the U.S. National Academy of Sciences called for "a broad moratorium on all recombinant experiments until they could be better reviewed by the scientific community". Subsequently, recombinant DNA research was permitted under safety guidelines established by the National Institutes of Health in mid-1976[18].

Similarly, current practices in treatment of degenerative diseases may one day seem bizarre, if the prospects for therapeutic cloning technologies, developed with due regard to ethical acceptability and safety issues, are realised.

Recommendation 2:

Council strongly supports the view of the Australian Health Ethics Committee that the *Minister for Health and Aged Care should encourage and promote informed community discussion on the potential therapeutic benefits and possible risks of the development of cloning techniques.*

The way ahead

For Australia to participate fully in and capture benefits from recent progress in cloning research, it is necessary to revise the 1996 NHMRC *Ethical Guidelines on Assisted Reproductive Technology*, which, while appropriate when they were written, have since been overtaken by unforeseen advances in biomedical research.

Restrictive legislation regarding reproductive technology would need to be repealed in some States, in the context of national regulatory arrangements binding on both publicly and privately-funded research. Such regulations should be set so as to allow the safety concerns as well as the benefits to be defined.

This action would permit work to commence on the scientific challenges in achieving the goal of tissue and organ repair in humans. While somatic nuclear replacement in an enucleated oocyte provides one starting point for tissue repair, alternative technologies may include:

- full or partial reversal of differentiation of adult cells;
- isolation and culture of dispersed stem cells known to exist in the adult animal;
- culture of primordial germ cells; or
- culture of ES cell lines that may be subsequently coaxed into a particular pathway (eg muscular, neuronal, endocrinal, immune or haematopoietic) of differentiation.

ES cells have been cultured in non-human primates[19] as have ES cells in humans, by isolating cells from the inner cell mass of human blastocysts[20] or by isolation of human primordial germ cells[21]. In the mouse, ES cells can be coaxed into specific lineages, showing aspects of vascular, muscular and neuronal differentiation[22] and have been successfully

Stem cells have the potential to contribute to replacement therapy in tissue repair…

when more is known about cell growth factors and their receptors.

transplanted, with functional integration, into fetal and adult mice[23]. The potential for stem cells to contribute to replacement therapy in tissue repair has been demonstrated by the ability of fetal-derived human neural stem cells to give rise to different types of nerve cells when transferred to the mouse[24] or rat[25] brain.

There may be safety concerns relating to some of these possible strategies for tissue repair, such as the possibility of deleterious mutations or loss of genomic imprinting in human stem cell lines grown *in vitro* for any length of time.

The possibility of partial reversal of differentiation of a person's somatic cells to form regenerative stem cell types may be preferred, from certain religious viewpoints, to the complete reprogramming of a person's somatic cells. This route will not be available until a great deal more is known about cell growth factors and their receptors, and, even then, may not be available for all types of tissue repair. Furthermore, research in one of the identified approaches (say, in ES cells) may inform research in other areas, such as in stimulation of dispersed, partially-committed stem cells.

There are two potential inhibitors to progress in biotechnology research in Australia.

Council is of the view that there are two potential inhibitors to progress in biotechnology research in Australia. One is unduly restrictive legislation based on misunderstanding of the benefits and risks; the other is the possibility of a public backlash against science if sensitive cultural issues are ignored by private or public scientific work. Appropriate regulation is needed.

Recommendation 3:

If Australia is to capitalise on its undoubted strength in medical research, it is important that research in human therapeutic cloning is not inhibited by withholding federal research funds or prevented by unduly restrictive legislation in some States.

Recommendation 4:

It is essential to maintain peer review and public scrutiny of all research involving human embryos and human ES cell lines undertaken in Australia. Council supports the view that a national regulatory two-tier approval process be adopted. Approval to undertake any research involving human embryos and human ES cell lines would need be obtained from a duly-constituted institutional ethics committee (IEC) prior to assessment by a national panel of experts, established by the National Health and Medical Research Council, on the scientific merits, safety issues and ethical acceptability of the work.

Conclusions

With respect to reproductive cloning to produce human fetuses,

Council considers that reproductive cloning to produce human fetuses is unethical and unsafe and should be prohibited.

With respect to research using human ES cell lines for the cloning of human tissues,

Council is of the opinion that human cells, whether derived from cloning techniques, from ES cells, or from primordial germ cells should not be precluded from use in approved research activities in cellular and developmental biology.

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Annex 2: The Australian Response to Cloning Techniques

Australian Federal Government

On January 14, 1998, the Federal Minister for Health and (then) Family Services, Dr Michael Wooldridge, issued a press statement giving an assurance that the Federal Government would "pursue ways of trying" to ensure that human cloning would not be undertaken in Australia. Dr Wooldridge acknowledged that the Commonwealth does not have complete power to legislate against human cloning, as this is a matter for the States and Territories, but stated that no public funds would be used for any type of research involving the cloning of human beings.

Dr Wooldridge affirmed that the Australian Government agrees with the UNESCO *Declaration on the human genome and human rights*, of which Article 11 states:

Practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted. States and competent international organizations are invited to cooperate in identifying such practices and in taking, at national and international level, the measures to ensure that the principles set out in this Declaration are respected.

Dr Wooldridge has asked the Australian Health Ethics Committee (AHEC) of the NHMRC to provide him with advice on:

- the potential and need for further pronouncement or possible legislation regarding the cloning of human beings;
- the need, and the appropriate model, for uniform legislation on human cloning in Australia.

The Australian Health Ethics Committee

On December 16, 1998 AHEC provided the Minister with advice on *Scientific, Ethical and Regulatory Considerations Relevant to Cloning of Human Beings*.

AHEC recommends that:

- the Commonwealth Government, through the Minister for Health and Aged Care, reaffirm its support for the UNESCO Declaration on the human genome and human rights;
- noting that Victoria, South Australia and Western Australia have legislation regulating embryo research and prohibiting the cloning of human beings, the Minister for Health and

Aged Care should urge the other States and Territories to introduce legislation to limit research on human embryos according to the principles set out in Sections 6 and 11 of the NHMRC Ethical Guidelines on assisted reproductive technology;

- noting that there are statutory authorities established in Victoria, South Australia and Western Australia which consider and may approve human embryo research under strict conditions, the Minister for Health and Aged Care should urge the remaining States and Territories to establish similar statutory authorities with power to regulate research on human embryos according to the principles set out in Sections 6 and 11 of the NHMRC Ethical Guidelines on assisted reproductive technology; and
- the Minister for Health and Aged Care should encourage and promote informed community discussion on the potential therapeutic benefits and possible risks of the development of cloning techniques.

Annex 3: The Current Regulatory Framework in Australia.

The 1996 NHMRC *Ethical guidelines on assisted reproductive technology* include guidelines on a number of practices of relevance to human cloning research. These are:

6.4 Non-therapeutic research which involves the destruction of the embryo, or which may otherwise not leave it in an implantable condition, should only be approved by an IEC in exceptional circumstances.

6.5 Protocols for ART (assisted reproductive technologies) in any clinic should take account of the success rates of fertilisation typically achieved in that clinic and, on that basis, seek to avoid the likelihood of production of embryos in excess of the needs of the couple.

The following practices are ethically unacceptable/prohibited:

11.1 developing embryos for purposes other than for their use in an approved ART treatment program.

11.2 Culturing of an embryo in vitro for more than 14 days.

11.3 Experimentation with the intent to produce two or more genetically identical individuals, including development of human embryonal stem cell lines with the aim of producing a clone of individuals.

In Australia, in addition to control provided by NHMRC guidelines, assisted reproductive technologies (ART) are regulated by specific regulation in three States, the Victorian Infertility Treatment Act (1995), South Australian Reproductive Technology Act (1995) and the Western Australian Human Reproductive Technology Act (1993). In each of these States, human cloning is an offence[(i)]. There is a system of self-regulation and accreditation involving the Reproductive Technology Committee (RTAC) and its Code of Practice for units using ART. In NSW, the New South Wales Law Reform Commission has recommended that human cloning should be prohibited, in a 1988 report, *Artificial Conception In Vitro Fertilisation* (NSWLRC 58, 1988). In NSW, there is draft legislation which makes human cloning an offence. Some Australian States have in place legislation or guidelines that refer specifically to *cloning*, but the term is not defined with any precision by the legislation.

NHMRC has also published Supplementary Note 7 to the NHMRC *Statement on human experimentation which states: Genetic manipulation of the germ (reproductive) cells of humans or fertilised ova is prohibited by this Supplementary Note.*

Annex 4: National Responses to Cloning Techniques.

The United Kingdom

The Royal Society has issued a policy statement, *Whither Cloning*[ii]. This learned statement gives a brief history of nuclear transplantation, reviews recent scientific developments in this area and identifies emerging scientific questions arising from cloning using an adult donor nucleus. The statement considers the repercussions arising from the technology and recognises that research into cloning in mammals could lead to important new insights into the function and control of cells. The Statement concludes:

with respect to cloning of human beings:

Council supports the view that reproductive cloning of humans to term by nuclear substitution is morally and ethically unacceptable and believes it should be prohibited.

with respect to research using ES cell lines for the cloning of human tissues:

any modification to existing legislation should be carefully drafted so as not to outlaw the potential benefits that could be derived from research on cloned embryos.

The **UK's Human Fertilisation and Embryology (HFE) Act** allows, under a licence from HFEA, research involving human embryos within strict limits which must not exceed the fourteenth day of their development. The HFEA's policy is that it will not license any research which has reproductive cloning as its aim. However, it would consider license applications for other types of research involving embryo splitting or nuclear replacement in eggs, provided that the research falls within one of the purposes of the HFE Act.

The Human Genetics Advisory Committee provides "a broad perspective on the implications of genetics"[iii] and reports to Ministers of the British government, while the Human Fertilisation and Embryology Authority has regulatory responsibility for the Human Fertilisation and Embryology Act, 1990. A working group consisting of both bodies was established to hold a consultation exercise on human cloning and advise government on whether the legislation needs to be strengthened in any specific way. In January 1998, the Human Genetics Advisory Committee (HGAC) and the Human Fertilisation and Embryology Authority (HFEA) issued a consultation document *Cloning Issues in Reproduction, Science and Medicine*[iv].

Following public consultation, the HGAC/HFEA advised[v]:

with respect to the cloning of human beings:

that the (UK) Government might wish to consider the possibility of introducing legislation that would explicitly ban human reproductive cloning.

with respect to research using ES cell lines for the cloning of human tissues:

the Secretary of State for Health should consider specifying in regulations two further purposes for which the HFEA might issue licences for research, so that potential benefits can clearly be explored. Firstly, the development of methods of therapy for mitochondrial disease and secondly the development of therapeutic treatments for diseased or damaged tissues or organs.

United States of America

On March 4, 1997, President Clinton directed that no Federal funds should be allocated for cloning of human beings. He requested the National Bioethics Advisory Commission (NBAC) to examine the legal and ethical implications of applying somatic nuclear transfer techniques to human beings. In an extensive report[vi], NBAC noted that while under current U.S. law, the use of somatic cell nuclear transfer to create an embryo solely for research purposes is already restricted in cases involving federal funds, there are no current federal regulations on the use of private funds for this purpose.

With respect to the cloning of human beings

NBAC could not reach a consensus on all the ethical issues regarding human cloning, advising that more widespread and careful deliberation was required, and suggested a moratorium on human cloning with a sunset clause of three to five years. NBAC recommended a moratorium because *current scientific information indicates that this technique is not safe to use in humans at this point.*

With respect to research using ES cell lines for the cloning of human tissues:

President Clinton has asked NBAC to undertake a thorough review of the issues associated with human stem cell research[vii]. Meanwhile, the federal agency, the National Institutes of Health, has ruled that it could fund research using human ES cells grown by privately-funded scientists[viii].

Annex 5: The International Response to Cloning Techniques

The United Nations and its agencies, and the Council of Europe have developed international standards intended to guide national standards for member and non-member States. These instruments do not impose binding legal obligations on Australia but international treaties and declarations are considered by courts of law as creating standards to be applied when interpreting domestic Australian legislation. There have been pronouncements on the cloning of human beings, the definition of a *human being* seemingly a matter for member States.

UNESCO

The United Nations Educational, Scientific and Cultural Organisation (UNESCO) recently concluded the *Universal Declaration on the Human Genome and Human Rights*. The Report was adopted unanimously on November 11, 1997 by the 186 member States, including Australia. Australian High Court Judge, Justice Michael Kirby is a member of UNESCO's International Bioethics Committee which formulated the draft Declaration. Article 11 of the Declaration, cited by Minister Wooldridge in his January 14, 1998 press release, states that "*reproductive cloning of human beings shall not be permitted*"[(ix)].

WHO

The World Health Organization (WHO) issued a press statement on 14 May, 1997, stating that the Fiftieth World Health Assembly had adopted a resolution affirming that: "the use of cloning for the replication of human individuals is ethically unacceptable and contrary to human integrity and morality."[(x)]

The Council of Europe

The Council of Europe provided an Additional Protocol on 12 January, 1998, to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, on the Prohibition of Cloning Human Beings[(xi)]. Article 1 states:

1 *Any intervention seeking to create a human being genetically identical to another human being, whether living or dead, is prohibited.*

2 *For the purpose of this article, the term human being "genetically identical" to another human being means a human being sharing with another the same nuclear gene set.*

The Council of Europe was informed by the Report to the European Commission on "Ethical Aspects of Cloning" by the Group of Advisers on the Ethical Implications of Biotechnology (May 28, 1997)[(xii)].

Annex 6: Glossary

Blastocyst: a cluster of cells following early cleavage of the fertilised egg, consisting of outer cells that have the potential to form placenta and an inner cell mass with the potential to form an embryo. The first signs of the embryo appear as the primitive streak, about 14 days after fertilisation.

Blastomere: any one of the cells into which the fertilised egg divides.

Cellular cloning: the process by which cells derived from the body are grown in tissue culture in a laboratory. The genetic makeup of the resulting cloned cells (the "**cell line**") is identical to that of the original cell.

Chromosomes: nucleic acid-protein structure in the nucleus of a cell. Chromosomes carry the heredity factors, genes, and are present in constant numbers in each species. In man, there are 46 in each cell, except in the mature ovum and sperm where the number is halved. A complete set of 23 is inherited from each parent.

Cloning: production of a cell or organism with the same nuclear genome as another cell or organism.

Cytoplasm: the contents of a cell other than the nucleus. Cytoplasm consists of a fluid containing numerous structures e.g. mitochondria that carry out essential cell functions.

Differentiation: an increase in complexity and organisation of cells and tissues during development.

Diploid: a cell such as a somatic cell having two chromosome sets, as opposed to the haploid situation of eggs and sperm which have only one chromosome set.

DNA: Deoxyribonucleic acid, found primarily in the nucleus of cells (some DNA is also found in mitochondria). DNA carries coded information for making all the structures and materials that the body needs to function.

Egg: the mature female germ cell; also called the **ovum** or **oocyte**.

Embryo: the developing human organism from the time of fertilisation until the main organs have developed, eight weeks after fertilisation. After this time the organism becomes known as a **fetus**.

Embryonic stem (ES) cell line: cultured cells obtained by isolation of inner cell mass cells from blastocysts or by isolation of primordial germ cells from a fetus. ES cells will not give rise to an embryo if placed in the uterus.

Enucleated egg: an egg from which the nucleus has been removed.

Fertilisation: the process whereby male and female gametes unite, beginning when a sperm contacts the outside of the egg and ending with the union of the male and female nuclei in syngamy to form the zygote.

Fetus: the term used for a human embryo after the eighth week of development until birth.

Fibroblast: a large cell common in developing or repairing tissues where they are concerned in protein and collagen synthesis.

Gene: a hereditary factor composed of DNA. Each of the body's approximately 100,000 genes carries the coded information that permits the cell to make one specific product such as a protein.

Genome: the complete genetic make up of a cell or organism.

Genomic imprinting: a small number of autosomal genes in the mammalian genome are inherited in a silent state from one of the two parents and in a fully active form from the other. The "imprinted" gene is silenced by methylation of the gene in one of the germlines and remains silent throughout embryogenesis. The process is thought to have a role in control of the rate of fetal growth.

Genotype: the genetic make up of an individual.

Germ cell: a reproductive cell precursor that will eventually give rise to a sperm or ovum. All other body cells are **somatic** cells.

Human reproductive cloning: the production of a human fetus from a single cell by asexual reproduction.

Haploid: the single chromosome set carried by the sperm and egg cells which are recombined after fertilisation to create the diploid chromosome set present in every cell of the body except sperm and eggs.

In vitro: in glass; referring to a process or reaction carried out in a test-tube or culture dish.

Mitochondria: cellular organelles that provide energy to the cell. The mitochondrion contains genes inherited exclusively from the mother.

Nuclear replacement: a technique which involves placing the nucleus from a diploid cell in an egg from which the nucleus has been removed.

Nucleus (*pl* nuclei): the central protoplasm of the cell that contains the chromosomes.

Oocyte: the mature female germ cell; the egg.

Phenotype: the visible expression of genotype.

Pluripotent: a cell or embryonic tissue capable of producing more than one type of cell or tissue.

Primordial germ cells: precursor reproductive cells in an embryo or fetus.

Somatic cell: any cell of an embryo, fetus, child or adult not destined to become a sperm or egg cell.

Stem cell: an undifferentiated cell which is a precursor to a number of differentiated (specialised) cell types. Stem cells may be totipotent, pluripotent, or committed to a particular cell lineage (eg neural stem cell).

Telomere: the tip of a chromosome. Loss of telomeres is thought to contribute substantially to ageing.

Telomerase: the enzyme that synthesises telomeric DNA.

Therapeutic cloning: medical and scientific applications of cloning technology which do not result in the production of genetically identical fetuses or babies.

Totipotent: the capacity to give rise to a complete embryo and its placenta.

Transgenic: containing a gene or genes introduced from another individual.

Xenotransplantation: a transplant from one species to another.

Zygote: the single-celled fertilised egg.

Endnotes

(i) Report on Scientific, Ethical and Regulatory Considerations Relevant to Cloning of Human Beings, AHEC, December 1998.

(ii) http://www.royalsoc.ac.uk/st_pol26.htm

(iii) Nature 389: 663, 1997

(iv) http://www.dti.gov.uk/hgac/papers/papers_c.htm

(v) http://www.dti.gov.uk/hgac/papers/papers_d.htm

(vi) http://bioethics.gov/cgi-bin/bioeth_counter.pl

(vii) http://bioethics.gov/clinton_letter.html

(viii) http://www.washintonpost.com (20.1.99)

(ix) http://www.unesco.org/ibc/uk/genome/projet/index.html

(x) http://www.who.ch/inf/pr/1997/97wha9.html

(xi) http://www.coe.fr/eng/legaltxt/168e.htm

(xii) Politics and the Life Sciences 16(2):309-312.