National Health and Medical Research Council
Australian Health Ethics Committee

Scientific, Ethical and Regulatory Considerations Relevant to Cloning of Human Beings

AUSTRALIAN
HEALTH ETHICS
COMMITTEE

GPO Box 9848
CANBERRA ACT 2601
TELEPHONE (02) 6289 5127
FACSIMILE (02) 6289 1327
ahec.nhmrc@health.gov.au

Hon. Dr Michael Wooldridge MP
Commonwealth Minister for Health and Aged Care
Parliament House
CANBERRA ACT 2600

Dear Minister

On behalf of the Australian Health Ethics Committee (AHEC), I have pleasure in presenting to you a response to your request for advice on the potential and need for further pronouncement or possible legislation regarding cloning of human beings.

AHEC established a Working Group to respond to your request for advice with respect to the cloning of human beings. The membership of this Working Group was as follows: Professor Don Chalmers (Chair), Dr Bernadette Tobin, Dr Peter McCullagh (both of the Australian Health Ethics Committee), Dr Wes Whitten (scientist) and Dame Margaret Guilfoyle DBE (member of the Council of the National Health and Medical Research Council).

The Working Group prepared a draft of the report it intended to send to you which was circulated for comment to a wide range of scientists, ethicists and persons knowledgeable in the area. A list of those individuals and organisations is listed in the Acknowledgement section of this Report. The Working Group chose not to conduct public consultation as so many International and National pronouncements from professional groups and community groups indicated a consensus of opinion on prohibiting the cloning of human beings.

In responding to your request, AHEC advises that a distinction must be drawn between the cloning of human beings which is ethically unacceptable (and legally prohibited in three States) and the cloning of such parts as DNA and cells. Cloning of DNA and cells is currently undertaken as part of routine laboratory research.

This Report recommends that you urge the remaining States and Territories (other than Victoria, South Australia and Western Australia) which have not legislated in this area to introduce legislation prohibiting the application of techniques to clone a new human individual. This legislation should not, however, interfere with those current cloning techniques which do not involve human embryos. This legislation should be drafted in such a way as to be consistent with the NHMRC *Ethical guidelines on assisted reproductive*

technology (1996) which permit non-therapeutic research on embryos only in exceptional circumstances.

Developments in this area are advancing in an accelerating fashion. During the period in which this Report was prepared, advances in embryonal stem cell research were reported by teams working at Wisconsin University and John Hopkins University in the United States. For this reason you may wish to consider requesting AHEC to report again on this matter after a period of three years.

On behalf of AHEC, which approved the Final Report, and its Working Group, I present this Report and trust that it contributes to the responsible development of science, and to informed community debate, in this complex area.

Yours sincerely

PROFESSOR D.R.C. CHALMERS
Chair,
Australian Health Ethics Committee

16 December 1998

EXECUTIVE SUMMARY

E1 The Commonwealth Minister for Health and Aged Care requested the Australian Health Ethics Committee to advise him on the potential and need for further pronouncement or possible legislation regarding cloning of human beings. The Terms of Reference of this request are set out in a later section of this report.

E2 The Australian Health Ethics Committee set up a Working Group to consider the issues. In the course of its deliberations, the Working Group conducted a limited consultation and did not receive any support for the application of any technique with the aim of intentionally cloning an individual human being. Names of the individuals and organisations who responded to the Working Group's invitation are listed at Appendix 2.

E3 In Chapter 1 of this Report, the Australian Health Ethics Committee responds to the Terms of Reference and advises that:

- A basic distinction should be drawn between the cloning of a *whole* human individual and the copying (also referred to as "cloning") of the component *parts* of a human (such as DNA and cells);

- The cloning of individual human beings is prohibited by State legislation in Victoria, South Australia and Western Australia and is prohibited by National Health and Medical Research Council guidelines;

- Legislation should be introduced in the remaining States and Territories to regulate human embryo research and to prohibit research on human embryos except as it is permitted in the NHMRC's *Ethical guidelines on assisted reproductive technology*;

E4 In addition to recommending a regulatory framework to prohibit cloning of a human being, Chapter 1 discusses how basic research work may be supported, for instance by the establishment of a non-human primate facility.

E5 Chapter 2 outlines relevant scientific considerations and their potential for human application. Background embryology is sketched. Several techniques for cloning human embryos are outlined. Issues of technical applicability and feasibility are considered. This chapter outlines projected benefits of cloning techniques which have the potential for supporting transplantation and tissue and organ repair. Possible risks of these techniques are identified.

E6 Chapter 3 identifies a series of ethical issues associated mainly with cloning techniques involving human embryos. This chapter reflects on the possible objectives for cloning techniques involving human embryos, the circumstances in which such cloning may take place, the significance of such cloning in itself, as well as the public policy issues associated with permitting or prohibiting such cloning.

E7 Chapter 4 sets out the relevant Australian legislation and regulations which prohibit the cloning of human beings. The NHMRC *Ethical guidelines on assisted*

reproductive technology also prohibit 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.

This chapter also considers the issue of embryo experimentation which may be involved with some of the proposed techniques to clone human *parts*. Three Australian States have legislation governing research on human embryos and the NHMRC guidelines noted above are also relevant.

E8 Chapter 5 provides information on international regulatory frameworks. It should be noted that there is considerable international consensus that the intentional cloning of a human being is unacceptable.

E9 Chapter 6 sets out the following recommendations and resolutions in respect of an appropriate regulatory framework:

Recommendations to the Commonwealth Minister for Health and Aged Care

Recommendation 1

The Commonwealth Government, through the Minister for Health and Aged Care, should reaffirm its support for the UNESCO *Declaration on the Human Genome and Human Rights*, in particular Article 11, which states that:

> *Practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted. States and competent international organisations are invited to cooperate in identifying such practices and in determining, nationally or internationally, appropriate measures to be taken to ensure that the principles set out in this Declaration are respected.*

Recommendation 2

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.*

Recommendation 3

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*.

Recommendation 4

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.

Resolutions of the Australian Health Ethics Committee pending State and Territory Legislation

Resolution 1

The AHEC proposes that, until legislation is introduced in the remaining States and Territories, the AHEC will collect information from institutional ethics committees (IECs) in these States and Territories on IEC research approvals of projects involving the application of current cloning techniques to human embryos. This information will be obtained in the course of the IEC annual compliance reporting system that is currently in place.

Resolution 2

The AHEC proposes that, until legislation is introduced in the remaining States and Territories, the NHMRC should consider the establishment of an expert advisory committee to assist IECs which seek advice on the scientific aspects of research projects involving the application of current cloning techniques to human embryos.

ABBREVIATIONS

AHEC: Australian Health Ethics Committee of the National Health and Medical Research Council

ART: assisted reproductive technology

CSIRO: Commonwealth Scientific and Industrial Research Organisation

DNA: Deoxyribonucleic acid

ES Cells: embryonic stem cells

GIFT: gamete intra-fallopian transfer

ICSI: intra-cytoplasmic sperm injection

IEC: institutional ethics committee

IVF: in vitro fertilisation

NHMRC: National Health and Medical Research Council

NIH: National Institutes of Health

RTAC: Reproductive Technology Accreditation Committee of the Fertility Society of Australia

SA: South Australia

WA: Western Australia

UNESCO: United Nations Economic, Scientific and Cultural Organisation

Vic: Victoria

WHO: World Health Organization

TERMS OF REFERENCE

In providing advice to the Minister for Health and Aged Care, the Hon. Dr Michael Wooldridge MP, on the issue of cloning of human beings, the Working Group (under the aegis of the Australian Health Ethics Committee) will:

1. distinguish between the cloning of human beings and human tissue and identify the considerations for each technique;

2. identify potential risks and benefits as well as ethical considerations in approving the cloning of human beings;

3. examine the current state of the cloning of human beings nationally and internationally;

4. identify the current legislative position of cloning of human beings in Australia and the implications for the NHMRC *Ethical guidelines on assisted reproductive technology*;

5. recommend the appropriate regulatory framework

    - through uniform legislation; or

    - other further pronouncement; and

6. in accordance with the recommendations arising from TOR 5, recommend the most appropriate model of legislation or pronouncement.

In providing the above advice, the Working Group is to identify / consider:

- the current legislative position nationally and internationally on the cloning of human beings;

- guidelines and other codes or pronouncements on the cloning of human beings; and

- the ethical issues underpinning the potential support for cloning of human beings.

CHAPTER 1 - RESPONSE TO THE TERMS OF REFERENCE

Term of Reference 1 - Distinguish between the cloning of human beings and human tissue and identify the considerations for each technique.

1.1 There is an international consensus that a distinction should be drawn between two categories of cloning: cloning of a human being and copying (cloning) of human component *parts* (such as DNA and cells). The consensus is that it is unacceptable to undertake any procedure with the aim of cloning a human being. The international position is expressed in Article 11, *Universal Declaration on the Human Genome and Human Rights*, 1997, which states that:

> *Practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted.*

1.2 The copying (cloning) of DNA and cells has been carried out for many years by a range of techniques. Cloning or copying of DNA and/or cells has brought benefits to both science and medicine. Many benefits are well recognised and have been drawn to the attention of the Australian Health Ethics Committee (AHEC) during consultation with a group of eminent scientists.

1.3 The AHEC notes that the development of the techniques of somatic cell nuclear transfer and the isolation of embryonic stem cells may involve experimentation on human embryos and/or germ cells. For many years Australia has placed restrictions on research on human embryos. Research on embryos is governed by the NHMRC *Ethical guidelines on assisted reproductive technology* (NHMRC Ethical Guidelines).[1] These guidelines set out several principles which should govern research involving embryos (paragraphs 6.1- 6.4) and list a range of prohibited / unacceptable practices (Section 11) as follows:

Section 6: Research on embryos

6.1 Research on human embryos must take place within the limits prescribed by law. In those States and Territories where there is no relevant legislation such research may only take place according to these guidelines.

6.2 Embryo experimentation should normally be limited to therapeutic procedures which leave the embryo, or embryos, with an expectation of implantation and development.

6.3 Non-therapeutic research which does not harm the embryo may be approved by an IEC.

[1] National Health and Medical Research Council, *Ethical guidelines on assisted reproductive technology* (1996, AGPS).

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. Approval requires:

- *the likelihood of significant advance in knowledge or improvement in technologies for treatment as a result of the proposed research;*

- *that the research involves a restricted number of embryos; and*

- *the gamete providers, and their spouses or partners, to have consented to the specific form of research.*

Section 11: Prohibited / unacceptable practices

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

1.4 The Reproductive Technology Accreditation Committee (RTAC) of the Fertility Society of Australia has adopted these NHMRC Ethical Guidelines. RTAC oversees a system of self-regulation and accreditation for units using assisted reproductive technology and sets professional and laboratory standards for clinical practice under this system of accreditation. RTAC requires reproductive technology units to abide by the NHMRC Ethical Guidelines as a condition of their accreditation.

1.5 The AHEC has earlier identified a need for complementary assisted reproductive technology (ART) legislation in all States and Territories and notes that only three States (Victoria, South Australia and Western Australia) have enacted legislation on ART. All three States require that permission must be obtained from independent statutory authorities to carry out any research procedure on a human embryo. The New South Wales Government has indicated its intention to legislate in a similar manner.

Term of Reference 2 - Identify potential risks and benefits as well as ethical considerations in approving the cloning of human beings.

(a) Risks and benefits, as well as ethical considerations in relation to cloning of human beings

1.6 There is an international consensus against undertaking procedures with the intention of cloning a human being.

1.7 The possibility of using cloning techniques involving human embryos raises four broad sets of ethical considerations: the objectives or goals for the sake of which these techniques might be used, the circumstances in which these techniques might be developed, the significance of such cloning in itself, and the wisdom of policies which permit or prohibit such cloning.

1.8 In addition, ethical objections are also raised by serious concerns about the *safety* of the somatic cell nuclear transfer technique. This risk to *safety* cannot be quantified at this time because the technique is at an early stage of development and has not been applied to human beings. The Dolly experiment, for example, involved some 277 embryos created using the technique from adult mammary cells. Only 29 of these embryos developed to the blastocyst stage (see discussion on the scientific aspects in Chapter 2) and a number of lambs had major organ malformations.

1.9 Although there has been widespread condemnation of the intent expressed by some to attempt cloning of human beings, some commentators postulated that the somatic cell nuclear transfer procedure could be used to benefit infertile couples. A possibility is to incorporate the genetic material from a somatic cell of an infertile man into the enucleated oocyte of his wife or partner for the purpose of reproduction. Such a procedure is, however, prohibited by State legislation and the NHMRC Ethical Guidelines.

(b) Risks and benefits, as well as ethical considerations in relation to cloning human cells and tissues

1.10 The copying (cloning) of DNA and cells has been carried out for a number of years. There have been major advances in the cloning of DNA and cells that have resulted in demonstrable benefits for science and medicine.

1.11 AHEC has been informed that the cloning techniques discussed in Chapter 2 may have a number of potential benefits which are discussed later in Chapter 2. The copying (cloning) of DNA enables the study and understanding of human genes and inherited characteristics. Copying DNA also enables the production of human proteins used in the development of pharmaceuticals (for example, this is already achieved with insulin for the treatment of diabetes, and with erythropoietin and colony stimulating factors for use in transplantation and the treatment of leukaemia).

1.12 The copying of DNA and cells facilitates the production of human proteins, vaccines and pharmaceuticals for therapeutic purposes. There is promising research currently being undertaken with relevance to organ transplantation and muscle regeneration. The copying of DNA and cells also enables primary research to be conducted into human cell biology and biochemistry without the ethical and practical difficulties posed by the involvement of people in medical research.

1.13 Cloning techniques, such as somatic nuclear transfer technique, have been, and will continue to be, applied to research which enhances our understanding of basic cell biology and aging. These techniques may increase future options for improving health and well-being.

1.14 The AHEC further advises that in so far as research is carried out on DNA and cells, there are no ethical difficulties and such research is subject to current standards governing research. Where such research involves human embryos, State legislation in Victoria, Western Australia and South Australia and the NHMRC *Ethical guidelines on assisted reproductive technology* apply.

Term of Reference 3 - Examine the current state of the cloning of human beings nationally and internationally.

1.15 The AHEC did not identify any support for the cloning of human beings in Australia during the development of this Report. There was no report that cloning of human beings had been attempted in Australia. Internationally, there has been a uniform condemnation of any procedures undertaken with the intent of cloning human beings. It is clear that there is widespread national and international agreement that the cloning of human beings is ethically unacceptable.

1.16 The AHEC notes that there is some support in the scientific community for research using the techniques of somatic cell nuclear transfer and development of embryonic stem cell lines for purposes other than the cloning of human beings.

Terms of Reference 4 - Identify the current legislative position of cloning of human beings in Australia and the implications for the NHMRC *Ethical guidelines on assisted reproductive technology.*

1.17 The States of Victoria, South Australia and Western Australia have already enacted specific legislation prohibiting the cloning of human beings. (The Government of New South Wales has indicated that it means to do likewise.) This legislation, which applies to both public and private research and all ART facilities, is discussed in Chapter 4. The NHMRC Ethical Guidelines also apply although State legislation prevails.

1.18 In New South Wales, Queensland, Tasmania, the Northern Territory and the Australian Capital Territory research funded by the National Health and Medical Research Council must follow the NHMRC Ethical Guidelines. While it is possible that private research facilities in these States and Territories could undertake research on human embryos outside of the NHMRC guidelines, the AHEC has no evidence of such research or practices being undertaken in any private institution. It is worth noting that all ART facilities, be they privately or publicly funded, are required by the Reproductive Technology Accreditation Committee of the Fertility Society of Australia to comply with the NHMRC Ethical Guidelines.

Terms of Reference 5 and 6

Recommend the appropriate regulatory framework through (a) uniform legislation or (b) further pronouncement.

In accordance with the recommendations arising from Terms of Reference 5, recommend the most appropriate model of legislation or pronouncement.

1.19 The AHEC notes that the Commonwealth Government is already in strong agreement with the UNESCO *Declaration on the Human Genome and Human Rights*. The AHEC considers that it is desirable that the Commonwealth Government reaffirms its support for the UNESCO *Declaration,* in particular Article 11, which states that the practice of reproductive cloning of human beings should not be permitted.

1.20 In addition, the AHEC considers that it is unsatisfactory to have variations between the States and Territories on important issues such as embryo experimentation and the application of cloning techniques to human *parts* such as DNA and cells.

Legislation should be introduced in all States and Territories which sets out guiding research principles and establishes statutory authorities in all States and Territories to approve and monitor research and developments in this area. The AHEC considers that similar statutory authorities to those established in Victoria, South Australia and Western Australia should be introduced in the other States and Territories. It is desirable that the current and future statutory authorities develop integrated approaches to embryo research involving current cloning techniques. Consistent with current State legislation and *the* NHMRC Ethical Guidelines, such research should only be approved in exceptional circumstances where there is likelihood of a significant advance in knowledge or improvement in technologies for treatment.

1.21 The AHEC further proposes that the Minister make a statement in support of research involving the copying of DNA and cells, making clear that this research does not involve the cloning of a human being.

1.22 In considering the possibilities that cloning techniques and research using embryonic stem cell lines may potentially be applied to produce tissues or organs, the AHEC recommends that a non-human primate research facility be established in Australia to ensure that research is conducted on animal models before it is conducted on humans.

1.23 The Minister for Health and Aged Care should consider inviting the NHMRC to investigate establishment of a non-human primate facility to support research using cloning techniques and involving embryonic stem cells, understanding that this facility may also be of value to the associated disciplines of reproductive biology, gamete biology, endocrinology, immunology, primate management and veterinary care

1.24 The NHMRC should be invited to consider the value of such a facility but its establishment should not be a charge against current NHMRC funds. If the NHMRC considers that such a facility is desirable, new funding must be obtained.

1.25 The AHEC also proposes that the Minister encourage the promotion of informed discussion in relation to this area of research.

CHAPTER 2 – SCIENTIFIC CONSIDERATIONS AND POTENTIAL FOR HUMAN APPLICATIONS OF CLONING TECHNOLOGY

Introduction

2.1 Awareness of the scientific background is an essential pre-requisite to consideration of the ethics and the public policy issues associated with cloning. Serious analysis of the issues raised by the cloning of human beings has been complicated by the sensationalism of much of the journalism on the subject. This chapter attempts to distinguish between confirmed scientific data and speculation. To anticipate its content, proposals to produce new human individuals with a postnatal existence have been almost universally disavowed as unjustifiable and unethical by scientists with the technical competence to do so. The thrust of scientific endeavour is towards applying technology relating to cloning to achieve goals other than producing new persons. As a prelude to ethical consideration of human cloning and of technology relating to it, an outline of the background and content of that technology will be provided.

Summary

2.2 A brief outline of basic embryology will need to clarify the meanings of terms such as embryo, embryonic stem cell and embryoid body if they are to be used in ethical analysis. Practical technical approaches to cloning will be summarised as will the results of their application in different species. A brief overview of possible benefits of the application of cloning technology will be provided, in the context of any benefits likely to accrue from alternative approaches. This will be followed by an outline of some potential risks. Finally, an attempt will be made to identify reasonable safety precautions, in the light of those risks. The safety of any novel clinical procedure represents a major ethical issue and its consideration should be based on the best available information.

The Meaning of Cloning

2.3 Notwithstanding its derivation from a Greek root, the English verb "to clone" is a twentieth century invention. The word was devised to describe the action of generating a new biological entity (originally a botanical specimen) by *asexual* reproduction as distinct from its generation by the combination of two gametes. A secondary meaning has been attached to "clone" based on the most prominent attribute of any entity produced asexually, namely that it would be genetically identical with at least one other entity. In many situations, this secondary meaning has supplanted the original and the term "clone" is applied to any replicate, irrespective of the relevance of sexual or asexual reproduction, to its generation. Of the four techniques for cloning identified in para 23, it could be argued that microsurgical embryo splitting falls within the secondary rather then the original definition. In common use, the grammatical object associated with the verb "to clone" may be the biological subject to which the cloning procedure is applied, or the product of the procedure.

2.4 It is important to recognise that genetic identicality of two individuals does not ensure their phenotypic identicality. Phenotypic features invariably reflect the interplay of genetic endowment and environmental experience. Behavioural characteristics are even less predictable, on the basis of genetics, than is phenotype.

Scope of this Chapter

2.5 This chapter is concerned primarily with the cloning of mammalian species, including humans, and with the scientific background of the techniques that could be applied to this end. It will not examine the existing and possible uses of the cloning (in the sense of replicating) of subcellular structures such as DNA. The cloning, or copying, of human DNA into other species is likely to be of increasing importance for the production of human proteins with pharmaceutical use such as insulin and erythropoietin. Additionally, human proteins produced by cloning DNA will have applications in research and related technology, and they will be an essential feature of the development of human gene therapy.

2.6 Apart from their application in human medicine, cloning techniques are likely to be of benefit in animal production. Animal husbandry uses could range from augmenting the limited numbers of some endangered wildlife species to producing genetically identical animals for research (especially in species in which the time required for complete inbreeding would be prohibitive) and replicating elite animals (albeit at the risk of curtailing the genetic diversity of a breed). Cloning of scarce transgenic animals that have been designed to produce pharmaceutically valuable agents in their milk is likely to be undertaken in the near future. This was the rationale for developing the cloning techniques first successfully applied in the case of "Dolly" the sheep, although "Dolly" itself was not transgenic[2]. Some transgenic animals have been produced already with the intention of using them as a source of organs for xenotransplantation to human patients.

2.7 In order to provide a framework for subsequent consideration of the ethics of human cloning, identification of the ends that may be sought, and the means likely to be employed to attain them, provides a useful reference point. Proposals for the application of cloning techniques to generate new human subjects (embryonic, fetal or post-natal) not with cloning of human genes or cell lines will be considered. Nevertheless, there may be situations in which development of a cell line necessitates the production of a new human subject as a preliminary step.

The Technical Applicability, Feasibility and Limitations of Cloning

2.8 In considering the ethics of cloning human beings, and of any associated technology applicable to this goal, the likelihood that the technology will be utilised must be considered. This likelihood will often be influenced by factors which are neither scientific nor ethical. These include the desire of researchers to proceed, the availability (present or foreseeable) of the required technology, the cost (including opportunity cost) of its utilisation, any limitations to access imposed by affordability,

[2] Wilmut I, Schnicke AE, McWhir J, Kind AJ and Campbell KHSL, Viable offspring derived from fetal and adult mammalian cells. *Nature*,(1997, 385, 810-3).

and the comparative cost and availability of alternative techniques to achieve similar objectives.

2.9 In discussing possible applications of cloning to human beings, factors that may be relevant in assessing the feasibility of their attainment will be identified. An attempt will be made to estimate the probability that similar goals will be more readily attained by alternative, more successful, techniques. Alternative solutions to problems for which cloning has been proposed will be indicated, when they appear to be at least as likely to be attainable.

Background Embryology

2.10 Although there are many features of mammalian development common to embryos of all species, extrapolation across species should be undertaken cautiously because of inter-species biological variations. It is notable that *intra-species* variations can be marked. For example, embryonic stem (ES) cells have only been produced from one strain of mice on a regular basis and from another occasionally. Intra-species variation is likely to be much more readily detected if highly inbred strains within that species can be compared. There is potential for a similar degree of intra-species variation (albeit undetected) to occur in relation to experimental primate embryology. Early development of the mouse may be summarised as follows.

2.11 When an oocyte is fertilised, each gamete forms a haploid pronucleus, and the two pronuclei subsequently come together in syngamy to form the diploid nucleus of the zygote. This zygote cleaves into two blastomeres which then divide further into four, eight, and sixteen smaller blastomeres. Late on the third day, the blastomeres become sticky and compact together to form a morula which cavitates to form a blastocyst with those cells destined to form the embryo, as distinct from its placenta and membranes, constituting the inner-cell-mass. Mouse blastocysts lose their outer covering, the zona pellucida and then penetrate the endometrium and, like human embryos, implant interstitially in the uterus. As one stage in development, embryonic totipotential cells differentiate so that each cell becomes committed, and restricted thereafter, to development as a single germ layer, either endoderm, mesoderm or ectoderm. Once this commitment has been made, the cell will normally develop only into mature tissues that are derived from that class of precursor.

2.12 A spectrum of embryos, ranging from a single blastomere from the 8-cell stage to an aggregate of two or more embryos (chimaeras), can produce apparently normal full term offspring. If a single blastomere from a 16-cell embryo is cultured, an empty vesicle without an inner-cell-mass may develop. These vesicles could potentially be used as carriers for further differentiation of ES cells.

2.13 Most research techniques relevant to cloning prior to the 1990s were developed in mice. In the present decade, substantial progress has been made in extending knowledge gained in mice to other species, in particular sheep, marmosets, macaques and humans.

Embryos, Embryonic Stem Cells and Embryoid Bodies

2.14 Some account of the usage of these terms, and of variations that have occurred in that usage is required as a background to consideration of cloning. The terms have been applied in different contexts on the basis of the origins of the entities to which they refer, of their current morphological appearance and of their possible potential for further development.

2.15 An embryo has traditionally been defined as the product of the union of male and female gametes. However, in the light of progress in experimental embryology and assisted reproduction technology, more extensive definitions have been proposed. The usage adopted by an Australian Senate committee in 1986 (in the course of an inquiry into experimentation with human embryos) was shaped by the potential of the embryo: "*genetically new human life organised as a distinct entity oriented towards further development.*"[3] Another definition, determined by the refinement of novel techniques to initiate embryonic development, was formulated by the U.S. Congress. The embryo was defined as any organism not protected as a human subject under other laws "*that is derived by fertilisation, parthenogenesis, cloning or any other means from one or more human gametes or diploid cells.*"[4]

2.16 Embryonic stem cells were isolated from normal embryos following the demonstration that pluripotential cells could be derived from teratomas in some strains of mice. This earlier recognised cell type, termed embryonic carcinoma cells (ECC), had the capacity to differentiate into a variety of different tissues in a manner resembling that of normal embryonic development. Isolation of ES cells from normal mouse embryos was first reported independently in 1981 by two laboratories[5,6]. A decade after the first preparation of ES cells from mouse embryos, the isolation of pluripotential cell lines from the primitive gonads of mouse embryos that had implanted in the uterus was reported. These pluripotent cells were referred to as embryonic germ (EG) cells. Whilst EG cells bear many similarities to ES cells, recent human studies, summarised below, raise the possibility of some differences. A third source of pluripotential stem cell lines has been from parthenogenetic embryos. To achieve this mouse oocytes, parthenogenetically activated by exposure to ethanol, were allowed to proceed to the expanded blastocyst stage before removal of the inner cell mass (ICM)[7]. Similar parthenogenetic development occurs spontaneously from oocytes or from male germ cells in a few strains of mice.

2.17 The defining properties of both ES and EG cells are their capacity for prolonged proliferation with retention of their undifferentiated form (under suitable cultivation conditions) together with a stable developmental potential to give rise to derivative

[3] Senate Select Committee on the Human Embryo Experimentation Bill 1985. *Human embryo experimentation in Australia*. Parliamentary Paper no 437/1986.
[4] Marshall E, News. A versatile cell line raises scientific hopes, legal questions. *Science,* (282, 1014-5, 1998)
[5] Martin GR, Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. *Proceedings of the National Academy of Science, USA,*(78, 7634-8.1981)
[6] Evans MJ and Kaufman MH, Establishment in culture of pluripotential cells from mouse embryos. *Nature,* (292, 154-6, 1981)
[7]Robertson EJ, Evans MJ, Kaufman MH, X-chromosome instability in pluripotential stem cell lines derived from parthenogenetic embryos. *Journal of Embryology exp. Morphology., (*74, 297-309, 1981).

cells from all three embryonic germ layers (endoderm, mesoderm and ectoderm).[8,9]. Examples of the degree of specialised differentiation potentially attainable have been provided by reports of the production of a range of precursors of different blood cells[10] and of precursors of neurons exhibiting synaptic structures which are a feature of mature cells[11].

2.18 The major impact to date of ES cell lines on experimental biology has been their use as a vehicle for the introduction of novel genes into the germline of laboratory mice. The strategy for this manoeuvre, first reported in 1984 and since very widely applied in the production of transgenic mice, was to inject ES cells (which had previously been transfected with the gene to be introduced) into blastocysts of the chosen recipient strain.[12] This procedure results in the production of a proportion of offspring that carry the transgene in their genome. Selective breeding from these animals can be used to develop lines homozygous for the transgene.

2.19 As studies of ES cell lines have been extended into species other than mice and as different production techniques have been used, especially relating to the precise stage of embryonic development at which cells were removed from the source embryos, it has become clear that not all cell lines are equivalent in their potential. As indicated above, it is likely that genetic background has a significant influence on outcomes. A major difference has emerged between murine and primate ES cell lines in that the former apparently lack the capacity to give rise to trophectoderm (an essential component of placental tissue) whilst the latter possess it. In reporting the capacity of rhesus monkey ES cell lines to produce trophectoderm, Thomson *et al*, suggested that the primate cell lines which they had developed may have been derived from embryonic cells which were at an earlier stage of differentiation than the murine equivalent.[13] Certainly, one of the original reports of isolation of murine ES cells noted that trophoblast cells had already emigrated from the cultivated blastocyst before the inner cell mass (ICM) from which the cell line was derived was harvested.[6] In contrast to this observation, a later report in which the migration of labelled cells within the early mouse embryo was traced suggested that the ICM actually contributed to the trophectoderm.[14] Development of placental tissues from murine ES cells either in tissue culture or after implantation in a recipient mouse does not appear to have been reported. Strengthening the likelihood of genuine species differences between ES cells from mice and primates has been the observation of trophectoderm-

[8]Martin GR, Evans MJ, Multiple differentiation of clonal teratocarcinoma stem cells following embryoid body formation in vitro. *Cell*,(6, 467-74, 1975).
[9] Doetschman TC, Eistetter H, Katz M, Schmidt W & Kemler R, The *in vitro* development of blastocyst-derived embryonic stem cell lines: formation of visceral yolk sac, blood islands and myocardium. *Journal of Embryology exp. Morphology.*, (1985, 87, 27-45).
[10] Hole N, Graham GJ, Menzel U & Ansell JD, A limited temporal window for the derivation of multilineage repopulating hematopoietic progenitors during embryonal stem cell differentiation in vitro. *Blood*, (1996, 88 1266-76).
[11] Finley MFA, Kulkarni N & Huettner JE, Synapse formation and establishment of neuronal polarity by P19 embryonic carcinoma cells and embryonic stem cells. *The Journal of Neuroscience*, (1996, 16(3), 1056-65).
[12] Bradley A, Evans M, Kaufman MH & Robertson E, Letters to Nature. Formation of germ-line chimaeras from embryo-derived teratocarcinoma cell lines. *Nature* (1984, 309, 255-6).
[13] Thomson JA, Kalishman J, Golos TG, Durning M, HarrisCP, Becker RA & Hearn JP, Isolation of a primate embryonic stem cell line. *Proceedings of the National Academy of Sciences USA.*, (1995, 92, 7844-8).
[14] Winkel GK & Pedersen RA, Fate of the inner cell mass in mouse embryos as studied by microinjection of lineage tracers. *Developmental Biology*, (1988, 127, 143-56).

forming capacity in the first human ES cell line.[15] However, the absence of mention of this capacity in relation to the first human EG cell line[16] leaves open questions of the relative importance of species and preparation techniques in determining potential.

2.20 Uncertainty about the potential of individual ES cell lines has led to ethical concerns. In addressing these in a review on primate ES cells published shortly before reporting the development of human ES cells, Thomson wrote: *"It is not known whether human ES cells could form a complete, viable embryo by any method, but this possibility has raised the greatest concern about derivation of human ES cells. If it were possible to form a complete embryo from human ES cells, it would be possible to form multiple complete embryos. Although ES cells have the potential to differentiate to any cell in the body, ES cells are not the equivalent of an intact embryo. If a clump of ES cells was transferred to a uterus, the ES cells would not form a viable fetus."*[17] He noted, however, the report of Nagy *et al*., which described the production of viable mice which were completely derived from ES cells that had been aggregated together with artificially produced tetraploid embryos of a different mouse strain (which were incapable of progressing through development themselves but able to provide an environment in which ES cells could do so).[18] The authors noted earlier reports in which any fetuses that had been totally derived from ES cells had died in the perinatal period.

2.21 *Embryoid bodies* (EB). This term has been applied to aggregates of cells with characteristics indicative of origin from more than one germ layer (most commonly of embryonic ectoderm surrounded by endoderm with the former representing the ES cells). Naming of these structures reflects their morphological resemblance to the fetal portion of the 5-day mouse embryo.[19] Originally described in, or derived from, teratomas the formation of EBs from aggregation of ES cells has been more recently observed. EBs were first observed free in the spermatic veins draining human testicular teratomas.[20] Subsequently, they were reported to develop frequently when teratomas were passaged intraperitioneally in mice (a situation in which the transferred cells remained free floating)[19] and the *in vitro* production of EBs from pluripotent teratocarcinoma cells that had been introduced into suitable cultivation conditions was described.[21]

---

[15] Thomson JA & Marshall VS, Primate embryonic stem cells. *Current Topics in Developmental Biology*, 1998, 38, 133-65)

[16] Shamblott MJ, Axelman J, Wang S, Bugg EM, Littlefield JW, Donovan PJ, Blumenthal PD, Huggins GR and Gearhart JD, Derivation of pluripotent stem cells from cultured human primordial germ cells. *Proceedings of the National Academy of Science, USA*, (95 (23), 13726-31, 1998).

[17] Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS and Jones JM, Embryonic stem cell lines derived from human blastocysts. *Science*, (282, 1145-7,1998)

[18] Nagy A, Rossant J, Nagy R, Abramow-Newerly W and Roder JC, Derivation of completely cell culture-derived mice from early-passage embryonic stem cells. *Proc. Natl. Acad. Sci. USA., (*90, 8424-8, 1993)

[19] Stevens LC, Embryology of testicular teratomas in strain 129 mice. *Journal of the National Cancer Institute.*, (*23* (6), 1249-95, 1959)

[20] Peyron A, Faits nouveaux relatifs à l'origine et à l'histogénèse des embryomes. *Bull. Assoc. Franc. Etude Cancer, (28*, 658-81, 1939)

[21] Martin GR and Evans MJ, Differentiation of clonal lines of teratocarcinoma cells: Formation of embryoid bodies *in vitro. Proceedings of the National Academy of Sciences, USA* (72(4), 1441-45, 1975)

2.22 Detailed examination of the products of cultured EBs from murine teratomas revealed almost all of the cell types found in the tumour itself.[8,22] Among the highly differentiated cell types that have been observed to develop when mouse blastocyst-derived ES cells were allowed to differentiate into EBs in tissue culture were rhythmically contracting myocardium and blood islands containing blood cell precursors.[9]

Cloning Strategies Potentially Applicable to Humans

2.23 The significant advantages and limitations of the principal techniques (all of which are currently established in animal experimentation) which could be employed in the future cloning of human beings are summarised as follows for:

a) Somatic cell nuclear transfer to a mammalian oocyte is still at an early stage of development.[2] Success rates are low at present, but may improve considerably as the technology is refined. If this happens, a very large number of replicate individuals could be generated from any single pre-existing cell donor Somatic cell donors could be fetal or at any postnatal age, for, at present, the technique is considerably more successful with fetal donors. Wells *et al*., have suggested that success of the procedure might be even further improved with nuclei from ES cells.[23] A potential liability of this technique is that any individual cloned using the nucleus of a mature somatic cell may be encumbered with mutations already accumulated in the nuclear genome of the donor cell.

b) Embryonic stem cell lines could potentially be used to generate an unlimited number of replicate individuals. As the cell line has been produced from an embryo, none of the replicates produced from it would be a clone of a postnatal individual whose existence antedated the production of the cell line (unless the embryo that had been used to generate the ES cell line had itself been produced by somatic cell nuclear transfer from such a postnatal individual).

c) Embryo splitting using microsurgery is a well established procedure that is, technically, more readily achievable than either of the preceding procedures.[24] However, only a very limited number of cloned individuals could be generated from any one embryo and it would not be possible, using this technique alone, to produce copies of a pre-existing individual. The frequency of successful development of demi-embryos is less than that of the original undivided embryo and, consequently, one would be unlikely to obtain as many divided embryos as theoretically possible.

d) Parthenogenesis Oocytes may be triggered to commence differentiation, in the absence of a male gamete, by means of a variety of stimuli. This can occur as a

[22] Teresky AK, Marsden M, Kuff EL and Levine AJ, Morphological criteria for the in vitro differentiation of embryoid bodies produced by a transplantable teratoma of mice. *J. Cell. Physiol., (84,* 319-32, 1974)
[23] Wells DN, Misica PM, Day AM and Tervit HR, Production of cloned lambs from an established embryonic cell line: A comparison between in vivo- and in vitro-matured cytoplasts. *Biology of Reproduction, (*57, 385-93, 1997)
[24] Shelton JN, Reproductive technology in animal production. *O.I.E. Scientific and Technical Review,* (9, 825-45, 1990)

spontaneous event in the ovaries of some strains of mice with the production either of a teratoma or of diploid embryos which are able to implant in the endometrium and develop for a limited time but which fail to form an effective placenta.[25] Mouse oocytes have been successfully activated *in vitro* by brief exposure to alcohol.[26] The resulting parthenotes were diploid but incapable of forming an adequate placenta and continuing to develop.

Cloning Achievements in Mammalian Species

2.24 As indicated above, successful attempts to produce ES cell lines have been restricted to a very few strains of mice until quite recently. ES cells have provided the basis for incorporating new genes in the genome of various strains of mice to produce transgenic animals. The production of viable mice exclusively from ES cells, without assistance from other cells, has not been reported, although the production of mice of which all tissues have been derived from ES cells has.[27]

2.25 The development of ES cell lines was reported in rhesus monkeys in 1995,[28] in sheep in 1997[29] and in humans in 1998.[30,31] There has not been any report, or other indication, that any of the laboratories involved intend to use their ES cell lines to produce cloned individuals of these species.

2.26 Reports of the actual cloning of individual animals with the production of viable offspring (as distinct from the development of techniques *potentially* applicable to such cloning) relate to sheep and mice and have exclusively utilised somatic cell nuclear transfer. The first instance was the production of "Dolly", following the transfer of the nucleus from an ovine mammary gland cell to an enucleated oocyte.[2] This achievement had been preceded by the production of sheep cloned following the transfer of a nucleus from a cultured cell line.[32] "Dolly" was the sole lamb surviving to post natal life in 277 attempts. Subsequent examination of its DNA confirmed identicality with the mammary cell donor.[33] The second report to date of the successful production of cloned mammals using nuclear transfer from mature, differentiated cells, described the transfer of nuclei from cells of the murine cumulus

---

[25] Eppig JJ, Kozak LP, Eicher EM and Stevens LC, Ovarian teratomas in mice are derived from oocytes that have completed the first meiotic division. *Nature, (*269, 517-8, 1979)

[26] Robertson EJ, Evans MJ and Kaufman MH, X-chromosome instability in pluripotential stem cell lines derived from parthenogenetic embryos. *J. Embryol. exp. Morph.*, (74, 297-309, 1983)

[27] Nagy A, Rossant J, Nagy R, Abramow-Newerly W and Roder JC, Derivation of completely cell culture-derived mice from early-passage embryonic stem cells. *Proc. Natl. Acad. Sci. USA.*, (90, 8424-8, 1993)

[28] Thomson JA, Kalishman J, Golos TG, Durning M, Harris CP, Becker RA and Hearn JP, Isolation of a primate embryonic stem cell line. *Proc. Natl. Acad. Sci. USA.*,(92, 7844-8, 1995)

[29] Wells DN, Misica PM, Day AM and Tervit HR, Production of cloned lambs from an established embryonic cell line: A comparison between in vivo- and in vitro-matured cytoplasts. *Biology of Reproduction*, (57, 385-93, 1997)

[30] Thomson JA and Marshall VS, Primate embryonic stem cells. *Current Topics in Developmental Biology*, (38, 133-65, 1998)

[31] Shamblott MJ, Axelman J, Wang S, Bugg EM, Littlefield JW, Donovan PJ, Blumenthal PD, Huggins GR and Gearhart JD, Derivation of pluripotent stem cells from cultured human primordial germ cells. *Proceedings of the National Academy of Science, USA*, (95 (23), 13726-31, 1998)

[32] Gearhart, J. New Potential for human embryonic stem cells, *Science*, (282, 1061-2)

[33] Ashworth D, Bishop M, Campbell K, Colman A, Kind A, Schnieke A, Blott S, Griffin H, Haley C, McWhir J and Wilmut I, DNA microsatellite analysis of Dolly. *Nature, (*394, 329, 1998)

oophorus (non-gametic cells surrounding the oocyte) to enucleated oocytes of mice.[34] Whilst substantial numbers of offspring were produced using this procedure, the success rate, expressed as live offspring per treated oocyte replaced in the reproductive tract remained low, of the order of 1 in 100.[35] In relation to the low success rates with somatic cell nuclear transfer, Wells *et al.*, have suggested that improved outcomes might be achieved if ES cells were used as a nuclear source because they may be more readily reprogrammed.[36]

Projected Benefits from Cloning and Cloning-Related Technologies

2.27 Benefits to be anticipated from the production of human ES cells were suggested recently as including "*in vitro* studies of normal human embryogenesis, abnormal development (through the development of cell lines with targeted gene alterations and engineered chromosomes), human gene discovery, and drug and teratogen testing, and as a renewable source of cells for tissue transplantation, cell replacement, and gene therapies."[32] To these might be added the acquisition of new information about nuclear-cytoplasmic interactions relevant to studies of ageing and cancer.

Assisting in Reproductive Technology (ART) Programs

2.28 Speculative initiatives to clone human beings could be classified either as projects which have as their ultimate aim the production of a child, a fetus or an embryo, or as projects directed instead to the production of some other end product or resource that would not be perceived as a new human subject, for example a cell line. There are also situations in which overlap between these two classes could occur. For example, an extension could be envisaged of the well publicised case in which a child was conceived in the conventional manner and successfully used as a histocompatible bone marrow donor for a pre-existing sibling with leukaemia. In this hypothetical extension, a new individual could be cloned by nuclear transfer from a cell collected from a pre-existing person who required transplantation of a renewable tissue. The new individual could then provide a source of tissue.

2.29 Whilst this chapter is concerned with identifying and summarising scientific information which may be germane to consideration of ethical issues raised by human cloning, it attempts, in doing this, to take account of the probability that any specific course of action will be adopted in practice. In this context, the comment in the submission of a leading Australian medical geneticist to the Working Group concerning cloning of humans and ART is apposite: "*we cannot imagine circumstances where reproductive cloning of humans is necessary for medical reasons*".

[34] Wakayama T, Perry ACF, Zocotti M, Johnson RK and Yanagimachi R, Full-term development of mice from enucleated oocytes injected with cumulus cell nuclei. *Nature*, (394, 369-74, 1998)
[35] R. Yanagimachi, Personal Communication, to W.K. Whitten.
[36] Wells DN, Misica PM, Day AM and Tervit HR, Production of cloned lambs from an established embryonic cell line: A comparison between in vivo- and in vitro-matured cytoplasts. *Biology of Reproduction*, (57, 385-93, 1997)

2.30 Taking account of the preceding comment, it could nevertheless be acknowledged that human cloning has been suggested as a means of broadening the scope of assisted reproduction. Both biological and social reasons have been advanced for cloning a human being by nuclear transfer. A possible medical ground for somatic cell nuclear transfer might be the wish of a couple, one or both of whom lacked gametes, to have a genetically related child. Transfer of a nucleus from a somatic cell of the male to a donated and enucleated oocyte might be combined with the female acting as the surrogate mother for the treated oocyte. A second suggested medical ground for the use of somatic cell nuclear transfer to a donated, enucleated oocyte might be prevention of transmission of diseases of mitochondrial inheritance. A technically similar procedure, which would *not* entail cloning, could also be applicable. This would entail the introduction of a maternal oocyte nucleus into an enucleated oocyte from a donor without activation of that oocyte. This "composite oocyte" could then be fertilised by a spermatozoon, either in the course of an IVF procedure or following its reintroduction into the maternal uterine tube.

2.31 Apart from the application of cloning techniques to circumvent infertility attributable to medical conditions, it has been proposed that they might be applied to avoid "infertility" imposed by normal biological processes. An example of such "social" application would be the use of somatic cell nuclear transfer to enable a lesbian couple to produce a child who was related by nuclear genes to one and by mitochondrial genes, gestation and lactation to the other. In view of the considerable risk likely to attach to any individual produced by cloning, as reflected by the current success rates for somatic cell nuclear transfer in sheep and mice, there would not appear to be any scientific justification for attempting to apply this technique to human subjects. In addition to the very low success rates, major congenital malformations (including hydronephrosis, testicular hypoplasia, ventricular septal defect and cleft palate) were observed in more than half of the lambs reaching an advanced stage of gestation.[36] Presumably, any application of cloning procedures intended to produce a full term infant would be undertaken under conditions similar to those applied to the production of the first child resulting from IVF. In that situation, the attending physician informed the recipient of IVF embryos that if any serious abnormality was discovered "this would be dealt with by induced abortion."[37]

Potential Benefits for Transplantation from Cloning Human Cells

2.32 The availability of tissues and organs for transplantation, relative to the demand for these materials, has steadily decreased as transplantation procedures have become technically more successful and more widely practised. Over and above the increasing shortage of transplantable material, long term immunosuppression of the recipient is required because the transplanted tissue will be subject to attack by the recipient's immune system unless the donor has been an identical twin. The complications that immunosuppression brings, most notably a progressive increase in the incidence of malignancies in recipients with extended survival, are a significant disadvantage. In this respect, tissues from a haplotype-matched sibling have always afforded advantages in being less likely to be subject to immunological rejection and so less likely to mandate the same degree of recipient immunosuppression. Tissue

[37] Steptoe P, in A Matter of Life: the Story of a Medical Breakthrough". Edwards R and Steptoe P London, Hutchinson, P143. (1980)

from a genetically identical donor would be free from any risk of such rejection and, consequently, immune suppression of recipients would not be necessary. Cloning techniques have been advocated as a means of attaining two discrete transplantation goals. In the first place, they might help to alleviate the quantitative deficit of transplantable tissue. Secondly, they might present an opportunity of providing tissues genetically identical with the recipient and so not susceptible to rejection, thereby removing the requirement for immunosuppression.

2.33 One potential goal of developing human ES cell lines is to provide cells for transplantation that are not available from existing sources and are less likely to be developed by other strategies. As already indicated, cell lines with the potential to differentiate into various types of specialised mature cells for transplantation to patients deficient in those cell types could either be specifically designed to be immunologically compatible with each individual patient or could be intended for more general use by any recipient. In the latter case, the cells would be genetically unrelated to the recipient and general considerations of histoincompatibility affecting tissue transplantation would apply in the same way as occurs with conventional transplants from unrelated donors. Consequently, the cells would be subject to rejection by the recipient's immune system unless this was therapeutically suppressed.

2.34 If a specified genetic identity (for example, identicality with a prospective recipient) is not required for the ES cell line, then any embryo that is available (either as a result of an IVF procedure or following embryo flushing from the uterus after coitus and fertilisation) could be used. If, on the other hand, it is necessary that the ES cell line be histocompatible with a particular individual (in order to ensure its acceptance after transplantation without the need for immunosuppression of that recipient), then it would be mandatory that the embryo from which the starting cells were to be harvested should have been generated by a cloning technique such as somatic cell nuclear transfer, from the prospective recipient, to an enucleated oocyte (the "Dolly" experiment).

2.35 A possible hypothetical alternative source for an ES cell line (that is, other than an embryo produced in either of the two preceding ways) could be to stimulate a gamete so that it developed parthenogenetically producing totipotent cells capable of differentiation into the required cell type.

2.36 As an alternative to stimulating ES stem cells to differentiate into a specific type of cell or tissue, an embryo could be maintained *in vitro* beyond the stage at which implantation in the uterus would normally occur with the expectation that the required type of cell or tissue might arise in the course of differentiation. To accomplish this, growth of the embryo would have to be prolonged until the specialised stem cell type which was required had both evolved and could be identified during microdissection of the embryo. For example, the identification of precursor stem cells specific for the human nervous system in an embryo is unlikely to become feasible until late in the third week after fertilisation. The source of embryos to be used for this purpose could be from an embryonic stem cell line or a newly generated (IVF or uterine flushing) embryo.

2.37 Suggested potential applications of stem cell lines specific for single organ systems include transplantation to patients deficient in the mature forms of those cells and the production *in vitro* and the subsequent administration of "messenger" molecules with the specific capacity to direct the maturation, and organisation into formed, normal tissue of precursor cells already present in the patient. As noted above, immune suppression of the recipient would be a requirement for acceptance of transplanted stem cells. Products synthesised by stem cells could have an application in facilitating the repair of deficiencies of specialised cell types (for example, after spinal cord transection) by directing precursor stem cells already present in a quiescent state in the patient's injured tissues to differentiate into mature, functional cells.

2.38 A possible advantage, for transplantation, of stem cell lines with a restricted capacity to differentiate only into the cells normally occurring in a single organ system is that it might reduce the risk of development of mature cell types, inappropriate for the location in which the stem cells were implanted. To the extent that transplanted stem cells retained some capacity to differentiate into other mature cell types, additional to those which it was intended to establish in the recipient, the risk of growth of unwanted cells in an inappropriate location would exist. Whilst this may not be of concern with attempts to introduce transplanted stem cells into some anatomical locations, it could be potentially disastrous in others (such as the central nervous system) which were especially susceptible to malfunction as a result of proliferation of inappropriate cell types (producing, in effect, a foreign body).

2.39 Apart from stimulating the differentiation of ES cells to produce specific types of formed tissue *in vitro*, it may become feasible to introduce ES-derived stem cells specific for a particular organ into that organ of a recipient patient with the intention that their subsequent proliferation and differentiation, after transfer, could assist the function of that organ (for example, the transfer of cardiomyocyte precursors into a failing myocardium).

2.40 Whilst it can be anticipated that ES cells that have differentiated *in vitro* into cells specific for a particular type of tissue may generate in tissue culture an integrated population of the various cell types identical with that normally occurring in the body, the extent to which this will be achievable may depend upon the complexity of the tissue. Increased difficulty in generating a complex tissue such as renal parenchyma or cerebral cortex rather than more "homogenous" tissues such as cardiac muscle may be anticipated if the development of that more complex structure during normal embryonic and fetal life depends upon a number of factors that are difficult to mimic in tissue culture.

2.41 The present state of knowledge in relation to the control of development of most specialised tissues is still confined to interpreting the events that occur in normal development rather than attempting to mimic this *in vitro*. It is likely that "organiser" molecules secreted by one cell type with the ability to influence the development of adjacent cells are of major importance in development of specialised tissues. It may be necessary to establish several highly specific micro-environments in close physical proximity to each other if a complex tissue is to develop accurately. Hepatic parenchymal cells relate to the cells which constitute biliary canaliculi, neurons have to synapse with each other, renal glomerular cells need to be juxtapositioned with

blood capillary endothelial cells. One characteristic feature of the normal course of development of many specialised types of tissue in embryonic and fetal life is the initial production of an excess of cells, only a minority of which will be selected to survive in the fully differentiated tissue. "Overproduction" of specialised cells which are programmed to die unless they establish a specific contact with a neighbouring cell and/or express a specific type of surface receptor is a feature of the normal developmental process in many tissues (for example in the nervous and immune systems) and may present an obstacle to replication of the differentiation process *in vitro*.

2.42 The possibility that ES cells could be induced to develop into a whole organ *in vitro* appears to be much less than that of development of individual cells and less complex tissues. One major obstacle to the growth of an organ *in vitro* from ES cells is likely to be the difficulty inherent in facilitating migration of cells at the appropriate stages. Migration of precursor cells during normal organogenesis represents one of the most influential contibuting factors to the final construction of many organ systems. As examples, the germ cells that populate the mature ovary and testis are immigrants during fetal life and the lymphocytes that provide the "in house" immune system in the gut (and so provide a first line of defence against pathogens) migrate successively from "offshore" in the fetal yolk sac to the liver before eventually colonising the gut. The preparation of an *in vitro* system to mimic this sequence of highly specialised microenvironments and also to underpin migration of precursor stem cells between them at the correct stages of development appears very unlikely. Apart from the normal requirement for migration of less differentiated cells *between* different organs during development, migration of cells *within* an organ can be an essential component of maturation. For example, the complex arrangement of successive layers of different classes of neurons within the cerebellar cortex of the human neonate represents the result of differential rates of migration of different classes of cells in fetal life - the "fastest" cells migrate furthest from the original cell layer on the cortical surface leaving a relatively cell-free zone before the "next fastest" and so on. This process is readily disrupted by aberrations in metabolism in an intact fetus.

2.43 One solution that has been suggested to the challenge presented by growing tissues or organs derived from cloned human embryos as a source of transplants would be to modify the development of the embryo in such a way that the upper parts of the central nervous system did not develop normally. Experimental systems have been reported in amphibia as a consequence of which major malformation of the brain, resembling that observed in the human condition of anencephaly, can be induced.

2.44 Proposals to develop incompletely formed embryos/fetuses in order to grow a complex organ have not provided detailed information about the milieu in which their development to the point of use as tissue sources would be undertaken. Their extended development *ex utero* would require major developments in the technology of ectogenesis, including the preparation of adequate artificial placentation. At present, it would appear that the human embryo could continue to develop *in vitro* for up to three weeks without major deviation from normality (in comparison with development *in utero*), apart from their much earlier loss of the capacity to implant in maternal endometrium and develop an effective placenta. There has been some experimentation in which human fetuses of fifteen weeks gestation were removed from the uterus and attached to perfusion apparatus intended to substitute for

placentation.[38] Survival time was quite limited. There has been nothing to suggest that any reasonable prospect exists, in the foreseeable future, for the development of technology to replace the human uterus between the third and fifteenth week.

2.45 As indicated earlier, alternatives to some proposed uses of ES cells in transplantation are also the subject of active research. Discoveries using either approach may advance understanding and further research in the other. One of the most active areas relates to replacement of neurons damaged by disease. As already indicated, neurons with some functional characteristics have been produced from murine ES cells.[11] Paralleling this, a number of laboratories have identified neuronal precursor cells in the brains of adult mice and some of the conditions necessary for the further differentiation of these cells have been identified[39,40]. Commenting on their results, one of these laboratories surmised that: "*identification of factors that induce or inhibit the in situ proliferation and differentiation of these cells may allow for their eventual manipulation in the intact adult mammalian CNS to replace cells lost to injury or disease*". Very recently, it has been reported, for the first time, that some neurons in the adult human brain retain the capacity for all division (an observation coincidentally discussed in the same issue of *Science* which carried the report of the first human ES cell line[41]). Similarly, in another field of very active research, the derivation of multipotent haemopoietic stem cells from a murine ES cell line[9] has been paralleled by the identification of cells with similar potential in adult mouse bone marrow.[42]

2.46 A consideration which applies to proposals for transplantation to replace cells damaged by disease, irrespective of whether they are prepared from ES cell lines or from cells obtained from other sources, is the extent to which the transferred cells may also be damaged by the disease process. There may be major differences between the response in different transplantation situations. For example, the most recent review of the outcome of pancreatic islet transplantation to diabetic patients noted that less than 10% of recipients had achieved insulin independence.[43] In an earlier review by the same author the point was made that control of the autoimmune process underlying juvenile diabetes, rather than islet cell transplantation, should be the objective: "*Our personal goal as transplanters should be obsolescence*".[44] On the other hand, the transplantation of dopamine-producing neurons as therapy for Parkinsonism has produced a measure of stable improvement in some patients and may ultimately find a place in regular clinical practice.[45]

---

[38] Lerner U, Saxena BN and Diczfalusy E, Extracorporeal perfusion of the human fetus, placenta and foeto-placental unit. *Karolinska Symposia on Research Methods in Reproductive Endocrinology,* (*4*, 310-25, 1971)
[39] Reynolds BA and Weiss S, Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. *Science,* (*255*, 1707-10, 1992)
[40] Richards LJ, Kilpatrick TJ and Bartlett PF, *De novo* generation of neuronal cells from the adult mouse brain. *Proceedings of the National Academy of Science USA* ,(*89*, 8591-5, 1992)
[41] Barinaga M, News of the week. New leads to brain neuron regeneration. *Science,* (282, 1018-9, 1998)

[42] Spangrude GJ and Johnson GR, Resting and activated subsets of mouse multipotent haematopoietic stem cells. *Proceedings of the National Academy of Science USA*, (87, 7433-7, 1990)
[43] Sutherland DE, Gruessner AC and Gruessner RW, Pancreas transplantation: a review. *Transplantation Proceedings*, (30, 1940-3, 1998)
[44] Sutherland DE, Pancreas and islet transplantation: now and then. *Transplantation Proceedings*, (28,.2131-3, 1996)
[45] Wenning GK et.al, Short-and long-term survival and function of unilateral ultrastriatal dopaminergic grafts in Parkinson's disease. *Annals of Neurology*, (42, 95-107, 1997)

Potential Risks Associated with Cloning Technologies

2.47 Attention has already been drawn to the potential risks of increased frequency of serious congenital malformations in offspring produced by somatic cell nuclear transfer.[2] [23] Concerns often attend the introduction of new techniques. As the introduction of ES cell technology has not been trialled on humans it is too early to make any reasonable estimate on the potential risks of this procedures. The NHMRC *Statement on Human Experimentation* requires that where any new experimental procedure which may have long term effects is undertaken, appropriate provision is made for the maintenance of records to allow proper follow up studies to be conducted on the long term effects of new procedures.[47] For example, a working group of the Institute for Science, Law and Technology, has expressed some concerns about the safety of the intracytoplasmic sperm injection technique used in ART: "*With ARTs, experimental techniques have been introduced rapidly in many of the more than 280 ART clinics in the United States without sufficient prior animal experimentation, randomised clinical trials, or the rigorous data collection that would occur in federally funded studies.*"[48] It is reasonable to extrapolate from the experience of somatic cell nuclear transfer on animals and conclude that there are safety concerns in relation to these techniques. In a 1998 review, James Thomson, who developed the first reported non-human primate and human ES cell lines, expressed his concern in the following terms: *"The possibility of transplanting differentiated derivatives of human ES cells to treat specific disease raises questions of safety and efficacy. Malignant transformation of transplanted cells becomes a particular concern because of the probable long-term culture of ES cells before differentiation and transplantation.*"[30]

Testing on Non-Human Primates

2.48 The NHMRC *Statement on Human Experimentation* states that: "The research protocol should demonstrate knowledge of the relevant literature and wherever possible be based on prior laboratory and animal experiments".[46] The application of cloning techniques to humans may require preliminary testing on animals. Concerns have been raised in relation to the introduction of ES cell technology into human trials without adequate preliminary testing in suitable animal models Thomson has stated: "*Juvenile-onset diabetes, for example, is a serious disease, but pancreatic cancer is usually rapidly fatal. Long-term culture could well introduce subtle genetic changes, in spite of the karyotypic stability generally observed in primate ES cells. Therefore, testing of the transplantation of specific cell types in an animal model before human clinical use would be absolutely essential and rhesus ES cells and rhesus monkeys would provide an accurate animal model for this testing. Indeed, in the example mentioned, Parkinson's disease and diabetes mellitus, extremely accurate models are available in the rhesus monkey*".[30] A similar concern was expressed in a review from a fertility clinic in the Netherlands about intracytoplasmic sperm injection: "*No experimental models preceded its introduction, partly because animal models were*

[46] National Health and Medical Research Council, Statement on Human Experimentation 1992 (AGPS) – Principle 4.

thought to be unsuitable and partly because of its immediate and overwhelming success."[47]

2.49 On the other hand, there are contrary points of view to the need for non-human primate research. For example, the contrary view has been expressed by an Australian researcher: "*In the area of ES cells there would seem now to be little rationale to concentrate on non-human primates rather than humans*". Work "*in monkeys or apes is very difficult and extremely expensive*". A number of submissions received by the Working Group were critical of the value of non-human primate studies for their research. Although the arguments presented related to the value of these studies as a contribution to basic knowledge, none addressed the safety issues raised by Thomson. The issue of the value of, and need for, non-human primate use in basic research, and in safety testing, need to be addressed. The safety of any novel clinical procedure represents a major ethical issue and its consideration should be based on the best available information. In view of the safety considerations raised in para 2.47 - 2.49, the issue of making facilities available to Australian researchers for non-human primate research has been examined (Appendix 1).

[47]te Velde ER, van Baar AL andvan Kooij RJ, Commentary. Concerns about assisted reproduction. *The Lancet*, (351, 1524-5, 1998)

CHAPTER 3 - ETHICAL ISSUES

Introduction

3.1 It is sometimes assumed that ethics is either a matter of individual preference or that it is always relative to the conventions of a particular society. Ethical issues can be extremely difficult and challenging and in an important sense they are irreducibly personal. None the less the assumption which informs this chapter is that ethics is something about which we can reason. Its specific subject matter concerns how we ought to live as individuals in a society. It is true, however, that there is often plenty of room for disagreement in the analysis and resolution of ethical issues. The aim of this chapter is to identify, in relatively summary form, a series of ethical issues associated with human cloning.

3.2 What is a satisfactory way to reason about the ethics of human cloning? Several approaches are at best incomplete. First, it is sometimes claimed that ethics involves *no more than* a calculation of the likely *consequences* (the 'benefits' and 'harms') of a proposal. But though consequences matter, and though it is often irresponsible not to consider them, they are not all that matter: sometimes a proposal ought to be rejected for what it is *in itself*, whatever its consequences. A second suggestion is that solutions to ethical problems can be derived by recognising the relevance in particular circumstances of a few broad *duties* (in bioethics, respect for autonomy, non-maleficence, beneficence and justice). But, though such duties express important ethical considerations, this suggestion begs many questions about the specific obligations these duties impose in particular circumstances. Thirdly, it is sometimes claimed that ethics is *no more than* a matter of deciding who has a *right* to do what to whom. But restricting one's attention to questions of rights, important though such questions are, almost always ensures that questions about the ethical acceptability of a particular proposal (to which it is claimed someone has a right) are ignored or avoided.

3.3 The approach adopted in this chapter is that reflection on the ethics of proposals to engage in human cloning needs to be sensitive to *all* of the following issues:

a) the wisdom of a variety of *objectives or goals* for which cloning might be pursued as a means: for instance, as a way of investigating human biology and pathology, as a way of increasing the number of embryos available for implantation in reproductive technologies, as a way of producing transplantable human organs and other tissues, as a way of producing valuable human proteins and pharmaceuticals, etc.;

b) the *circumstances* in which cloning might take place: for instance, whether or not cloning techniques have been tested on animal models prior to being tested on humans, whether or not advances in human reproductive technologies would require destructive research on human embryos, how safe the techniques for cloning could reasonably be judged to be;

c) the significance of cloning *in itself*; and

d) the likely *consequences* of a social policy which permits cloning in some circumstances but not in others or of a policy which prohibits it altogether.

Terminology

3.4 Earlier (2.1) a distinction was drawn between (a) applications of cloning techniques to generate new human subjects and (b) applications of cloning techniques to generate human genes or cell lines. Another, more general, way of expressing the same difference is to distinguish between (a) the (re)production of human *wholes* or (b) the (re)production of the component *parts* of a human. This discussion of the ethics of cloning focuses in the main on the ethical issues associated with the use of cloning techniques involving whole human entities, in particular embryos. Ethical issues associated with the production of "parts" are raised insofar as they involve "wholes".

3.5 Recognising a fundamental distinction between the cloning of a 'whole' human entity and the cloning of a component 'part' of a human being does not commit one to the idea that all the members of the first category are 'human beings' in an ethical or moral sense. It merely follows from the fundamental biological difference between copying a new individual of the human species identical to some other individual and copying components parts of an individual.

3.6 In this discussion of the ethics of cloning, it will be assumed (though not argued for) that proposals to employ cloning techniques on humans raise special ethical issues over and above those raised by proposals to employ cloning techniques on non-human animals and on plants (significant though these ethical issues are in themselves). [48]

3.7 One final preliminary. Earlier (in 2.3), reference was made to the two usages of the word 'clone': an older usage and a more recent usage. In the older usage the key idea was the *method* by which clones are produced, namely by asexual reproduction. In the newer usage, the key idea is the *resulting property* of a clone, namely that it is genetically identical with at least one other biological entity. In this chapter the difference between these two usages will emerge as ethically significant.

The ethical significance of the objectives sought through cloning

3.8 There are various objectives towards which cloning techniques involving human embryos may be a means. Several deserve their own consideration.

A To investigate and understand human biology and pathology:

3.9 Knowledge and understanding are good in themselves. However there are both ethical and unethical ways of advancing knowledge and understanding. Many countries have worked out their own codes of ethics to regulate research, especially that relating to humans.

[48] However it should be stated that this widely-shared assumption is challenged both by some schools of moral philosophy and by the practical overlap, of techniques and personnel, between reproductive technologies in animal husbandry and reproductive technologies in human reproduction.

3.10 It would be out of place in a chapter on the ethics of cloning to rehearse all the principles enunciated in such codes. However it is relevant to draw attention to one ethical principle which requires the undertaking of research on relevant animal models before it is conducted on human subjects. Programs of assisted reproductive technology (responsive as they often are to commercial pressures) have sometimes been insufficiently attentive to this ethical requirement on research on human embryos.

3.11 There is, of course, much debate in the scientific community about the species of animals most suitable for such research and indeed about the kinds of research which ought to be conducted on animal models prior to being conducted on humans.[49] Ultimately, however, the development of cloning techniques for use in human reproductive programs will require experimentation on human embryos. At some point techniques developed in non-human animals will need to be made to work on humans. Then new ethical questions will abound: How many human embryos may be experimented on and then destroyed? What degree of risk to embryos will be acceptable (if any)? To what stage of development may they be experimented on? If cloned human embryos are brought to term, what kinds of developmental abnormalities in these embryos (and their offspring) will be acceptable? Acceptable to whom? What will be an acceptable trade-off between 'certainty of normality' and 'numbers of embryos experimented on'?

B To assist in reproductive technology programs (by enabling a couple to have a child genetically related to one or both of them, or enabling a couple to avoid passing on a disease determined by mitochondrial genes, or increasing the number of embryos available for implantation, or enabling an individual or couple to avoid the 'infertility' imposed by normal biology, etc.):

3.12 Each of these objectives requires its own ethical evaluation.

3.13 The desire to have a child to whom one is genetically related is a deep and powerful human feeling and source of motivation. Many people would look sympathetically on a proposal to create an embryo using somatic cell nuclear transfer if that were the only way in which a couple could have child genetically related to at least one of them. Indeed, some have argued that this is the one scenario which would justify human cloning.[50] Nevertheless, other considerations need to be borne in mind. For instance, a child who developed from an embryo formed by nuclear transfer from his ‘father’ or ‘mother’ would not be a descendant of that person in the normal sense. And the question of whether the fulfilment of that desire is a sufficient reason to incur the risks involved in developing such an embryo also needs sober reflection.

3.14 The desire to have a healthy child is similarly a powerful desire and source of motivation. If creating an embryo by somatic cell nuclear transfer were the only way for a couple to ensure to avoid passing on to their children a disease determined

[49] There is also debate about whether Australia should have its own animal research facilities and programs and, if so, how such animals should be acquired and managed, how their welfare is best looked after, what laboratory facilities and infrastructure are needed, and what would be an adequate budget allocation for the purchase and maintenance of such animals. See Appendix 1.

[50] Strong C, Cloning and Infertility,*Cambridge Quarterly of Healthcare Ethics* (7:279-293, 1998)

by mitochondrial genes, then many people would believe that that technique would be justified in those circumstances. Once again, however, other considerations ought to be borne in mind. For instance, this proposal would avoid the need for the couple to use 'donor' gametes. On the other hand, deciding what should be a sufficient degree of genetic disease to justify risks to the embryo is an ethical issue on which opinions are likely to be divided.

3.15 Again, some couples may wish to increase the number of embryos available to them for implantation in assisted reproductive programs. Embryo splitting by microsurgery offers this potential. In addition, it may obviate the need for women who undergo IVF to be (re-)subjected to super-ovulants (with the possible associated increased risk of cancer of the reproductive tract). The weighing of these benefits against not only the risks to embryos but also against the expenditure of public funds on this response to infertility is also a matter on which opinions are divided.

3.16 Finally (though of course this is only a sample of the objectives for the sake of which cloning techniques involving human embryos might be seen as a means), the 'infertility' imposed by normal human biology on single women, women in lesbian relationships, etc., might be circumvented by the technique of somatic cell nuclear transfer. However many would question whether it is just to a child deliberately to bring him or her into the world outside the social setting of a family in which there is both mother and father.

C To produce transplantable organs and tissue:

3.17 This objective is a laudable one in itself. The two main problems which have beset transplantation programs - the lack of a sufficient supply of organs and tissue and the problems associated with long term immunosuppression - have already been set out (in 2.33 to 2.46). Cloning techniques seem to offer, at least in theory, answers to both of these problems. If cells, organs and tissues could be produced by the development of embryonal stem cell lines, the absolute shortages in the supply of these resources could be overcome, a source of histocompatible organs and tissues could be provided and the need for long term immunosuppression avoided. However, acceptance of such a process raises the ethical issues often referred to as 'slippery slope' issues (that is, that in the acceptance of research on human embryos in order to produce desired tissues and organs an irreversible step may be taken that will lead to scientific advances that in turn will make the cloning of human beings more likely to be accepted).[51]

D To produce valuable proteins and pharmaceuticals

3.18 The production, by cloning techniques, of some component parts of a human - in particular, human DNA and cell lines - has been a standard part of research and clinical practice in health care for over fifty years. Its benefits are significant and have been elaborated earlier (at 2.5 to 2.6).

[51] At the moment at least, such a method of producing of organs and tissues does not seem to have attracted the interest of transplant community (which is looking rather to xenotransplantation to take transplantation medicine into the twenty-first century).

E To copy a human being

3.19 The idea that anyone might want to use cloning technology to 'copy' a human being may seem too far-fetched to be worthy of serious consideration.[52] But perhaps it is worth considering whether people might have reasons to want to 'copy' existing human beings. At least two come to mind: (a) a couple might wish to establish a source of compatible tissue or organs for transplantation to an existing child or (b) a couple might seek to 'replace' a loved child who is dying or has died.

3.20 The first scenario raises difficult questions of personal identity: in what sense would a child raised from a cloned embryo stored for this purpose be a 'copy' of an existing child? In addition, the ethics of such a proposal need careful consideration. Some have argued that, since there has already been a well-publicised case of a child being conceived in order to establish a histocompatible bone marrow donor for an existing child with leukemia, there could be no objection to the production of a child by cloning techniques for this kind of reason. However there is debate about the ethics of this objective. Some think that it represents a failure to respect the new child's dignity and worth as a human being, that it involves treating it more as a means than as an end in itself, and that this 'failure' is not expunged by the parental love and affection the child is likely to receive as he or she grows up. Others think that what matters most is how the child is regarded and treated when it arrives.

3.21 The second scenario raises a relatively new idea in moral philosophy: the idea that a child is something that can be 'replaced'. Whilst it is true that the *place* that a child has in the life or lives of other(s) may be thought to be 'replaceable', the thought that an individual child *himself or herself* might be replaced is both mistaken (in that it involves the fallacy of genetic determinism) and runs against some of the deepest features of our shared sense of the significance of other human beings: it is not just that we cherish their individuality and irreplaceability in our affections; it is also that our moral sense of our responsibilities to others depends on a deep sense of their individuality and irreplaceability.

The ethical significance of the circumstances in which cloning takes place

3.22 As already noted, knowledge and understanding are good things in themselves. So too is the relief of suffering caused by infertility and the availability of a supply of histocompatible organs and tissues. However, none of these objectives is absolutely good in the sense that it may legitimately be pursued without regard to the ethical acceptability of the means employed towards it achievement and the circumstances in which it is pursued.

3.23 And so, consideration needs to be given to at least the following: (a) whether or not experimentation has been conducted on animal embryos prior to its being conducted on human embryos, (b) whether or not experimentation on human embryos will be therapeutic or non-therapeutic, destructive or non-destructive, (c) the techniques used in cloning, (d) the risks associated with proposed techniques. The first and the

[52] On the other hand, an American physicist has already publicised his entrepreneurial objective to do precisely that.

fourth of these considerations have been canvassed (the first at 2.48 - 2.49, the fourth at 2.47). The second and third need some thought in this chapter.

Whether or not advances in knowledge and clinical technologies will require experimentation on human embryos, in particular destructive experimentation on embryos.

3.24 On one view of the matter, some basic ethical considerations apply to research (in particular experimentation) and clinical practice on all human life even at its earliest stage of development. On another, research on human embryos does not raise the ethical considerations associated with research on other human subjects. This disagreement reflects different views of the status of the human embryo.[53]

3.25 A fundamental ethical distinction to be made with respect to experimentation on human embryos is the distinction between forms of research or experimentation which are therapeutic in intent and those which are non-therapeutic in intent. A therapeutic intervention is an intervention directed towards the well-being of the individual on whom the intervention is conducted. A non-therapeutic intervention is an intervention that is not directed toward the benefit of the individual on whom it is conducted but rather towards improving scientific knowledge or technical application. The latter may involve either destructive or non-destructive procedures.

3.26 Therapeutic research and experimentation on human embryos raises no unique ethical issues: it ought to be governed by the complex of ethical principles which govern all research on human subjects.[54] Non-therapeutic research is more contentious. Many jurisdictions have legislated to limit the practice of non-therapeutic research on human embryos. Such legislation differs in detail from jurisdiction to jurisdiction. Some jurisdictions permit such research only in exceptional circumstances and only for a relatively brief passage of time (for example, for 14 days). Though law is not a completely reliable guide to ethics, none the less the existence of laws regulating non-therapeutic research on human embryos (together with other regulations with the same intent) attest to a widespread recognition in many societies that even so undeveloped a 'human whole' as an embryo ought to be treated with a respect that reflects its human status. Non-therapeutic research on such vulnerable entities involves, on this view, a clear predisposition to treating them more as a means than an end in themselves and is thereby ethically unacceptable.

Techniques used in cloning

3.27 Earlier (2.23) a variety of cloning techniques was sketched: somatic cell nuclear transfer, the development of embryonic stem cell lines, embryo splitting and parthenogenesis. The ethical significance of each deserves some thought.

(a) Somatic cell nuclear transfer. There are several substantial ethical objections to cloning by somatic cell nuclear transfer. In the first place, because of the risks, at

[53] There are also differing views not only of the status of a human foetus but also of the status of a newborn human child.

[54] See however, te Velde ER, van Baar AL, van Kooij RJ, Concerns about assisted reproduction in *The Lancet* (351: 9115, 23 May 1998)

the very least it would be premature to permit this technique in human reproductive programs. Secondly, it threatens a confusion of identity and individuality. A child so produced would have the genotype of someone who had already lived, would not be fully a surprise to the world and, were this known by others (as it must be), he or she would be likely to be compared to his or her 'alter ego'. On the other hand, if his or her origins were kept secret from the child, this would violate his or her entitlement to knowledge of his or her own identity. On this view, somatic cell nuclear transfer, like other forms of eugenic engineering of the next generation, even in benevolent cases, represents a violation of the meaning of parent-child relations.

(b) Development and use of embryonal stem cell lines or 'embryoid bodies'. Earlier (2.21) it was noted that the term 'embryroid body' (which has been used for a long time in experimental embryology to refer to aggregates of cells (derived from tumours or from differentiations of germ cells) some of the features of which resemble those of an embryo) has, more recently, also been applied to aggregates of embryonic stem cells (and, sometimes, to embryos which lack the capacity for development to full term).[55]

The ethical significance of developing and using embryonal stem cell lines as a technique for cloning depends, in significant part, both on whether the technique involves experimentation on embryos and whether the experimentation would be therapeutic or non-therapeutic, etc. At the moment the answer to the first question may not be knowable with certainty. However the question of whether the development and use of such embryonal stem cell lines does involve experimentation on embryos ought not to be glossed over by the use of the term 'embryoid body' which (in this context) sometimes seems to imply that, in addition to embryos (whole entities) and aggregations of cells (component parts), there is some third kind of thing (called an 'embryoid body').

(c) Embryo splitting. Embryo splitting (by micro-surgery) mimics a process that already takes place spontaneously in nature. However its capacity to increase the number of embryos available for implantation is at present uncertain.[56]

(d) Parthenogenesis. The ethical objections noted above (to somatic cell nuclear transfer) would apply also to the use of parthenogenesis. However, this procedure is no more than a theoretical possibility.

The ethical significance of cloning *in itself*

3.28 Earlier (at 2.3), a shift in usage of the term 'clone', from the idea of asexual reproduction to the idea of genetically-identical individuals, was noted. Some

[55] This extension of the term relates more to the morphological features of the aggregates of embryonic stem cells than to their capacity for further development. Given the appropriate circumstances (sc. their being fused with a blastocyst), aggregates of cells derived from embryonal stem cells may have the potential to differentiate into embryos.

[56] 'Whether embryo splitting is clinically feasible and whether the expected benefits to infertile couples will outweigh its risks and possible misapplication is unknown at the present time and cannot be determined without further research.' Statement developed by the American Society for Reproductive Medicine's Ethics Committee and accepted by the Board of Directors on December 8th, 1995.

objections to the cloning of human beings are responses to cloning *as asexual reproduction.* Thus Leon Kass has argued that the rational idea which has been expressed emotionally in the widespread reaction of revulsion to the possibility of cloning human beings is a response to its involving asexual reproduction. Pointing out that human societies everywhere have structured child-rearing responsibilities and systems of identity and relationship on the bases of certain deep natural facts of begetting, and that these institutions are not cultural constructs alterable without human cost but rather reflections of human biology which have significant implications for human identity and equality, he claims that asexual reproduction is a major violation of a human being's nature as an embodied, gendered and engendering being, that *"[a]sexual reproduction confounds all normal understanding of father, mother, sibling, grandparents, etc. and all moral relations tied thereto."*[57] This objection to human cloning (which is, strictly, an objection to some but not all cloning techniques, in particular to somatic cell nuclear transfer) is associated with a wider objection to any proposal which seems to depersonalise human reproduction, any proposal which might seem to transform the 'begetting' of children into a process of their 'manufacture' as artefacts or commodities.

3.29 On the other hand, some of those who think that there is nothing especially troubling about proposals to clone human beings often start from the assumption that the term 'cloning' refers to *the production of an individual genetically identical to at least one other individual*.[58] They have pointed out that organisms which start out genetically identical to each other (that is, share the same genome) quickly become genetically distinct from each other (that is, acquire different phenotypes). Identical twins share the same genome but are recognisable as, and are treated as, individual human beings. However, even on this understanding of what a clone is, there is a difference between a clone which is deliberately so produced and a 'clone' which arises spontaneously in nature.

The ethical significance of a policy which permits or prohibits cloning in some circumstances

3.30 Finally, there is an important distinction between (a) reflection on the *intrinsic ethics* of a particular proposal on the one hand and (b) reflection on the *social consequences* of a policy which permits or prohibits proposals of that kind on the other. Proposals which would involve the use of cloning techniques on human embryos, whether for reproductive purposes, for investigative purposes or for purposes related to the supply of organs and tissues, have implications not only for the individuals directly involved but also for the society. Indeed it might be said that the ethical significance of both legislation and codes of ethics is as much related to considerations concerning the common good as it is to considerations relating to the proper domain of individual liberty. Thus, a consideration of the ethics of proposals to use cloning techniques on human embryos needs to be sensitive to questions about the likely *consequences*, both short and long term, of a social policy which permits human cloning in some circumstances but not in others.

[57] Kass L, The Wisdom of Repugnance, *The New Republic* (2 June 1997)
[58] Lewontin, R, The confusion over cloning, *The New York Review of Books* (16 November 1997)

3.31 With respect to public policy, there are three theoretical possibilities: (1) a policy which permits the use of cloning technologies involving human embryos quite generally, (2) a policy which prohibits the use cloning techniques involving human embryos quite generally, and (3) a policy which permits the use of these techniques in some circumstances (for instance, to enable an otherwise infertile couple to have a genetically-related child) whilst prohibiting it in others (for instance, to enable a couple to store an embryo in case a 'replacement' child were ever wanted).

3.32 There are different views of the wisdom of a policy which would permit the use cloning of techniques human embryos in some circumstances. Some have argued that it would be better to regulate such technologies by law than to drive research and clinical practice underground or offshore by prohibiting it. Others have pointed out that a policy which permits the use of such technologies in some circumstances whilst prohibiting it in others is likely to be beset by the problems associated with a 'slippery slope'. A consideration of ethics of cloning needs to be sensitive to such 'slippery slope' concerns. Would it be practically possible to legalise the use of cloning techniques involving human embryos in some circumstances and for some reasons but maintain a legal prohibition on the use of these techniques in other circumstances and for other reasons?

Summary

3.33 In this chapter, an attempt has been made to sketch some of the main considerations which should enter into reflection on the ethics of cloning. A distinction has been drawn between the cloning of human 'wholes' and the cloning of the component 'parts' of a human being. Most of the discussion has focussed on the ethical issues associated with various proposals to use cloning techniques in ways which involve human embryos. Four sets of considerations were elaborated: the objectives for which the use of such techniques may be a means, the circumstances in which the use of such techniques may take place, the significance of such cloning in itself and public policy considerations of permitting or prohibiting the use of such techniques. Overall, it has been suggested that the more convincing, weighty and cogent arguments support constraints on the use of cloning techniques which involve human embryos.

CHAPTER 4 - AUSTRALIAN LEGISLATION AND GUIDELINES RELEVANT TO CLONING IN EXISTENCE AT NOVEMBER 1998

Introduction

4.1 This chapter discusses current State legislation and NHMRC ethical guidelines[59] governing research which deal directly or indirectly with human cloning. The Reproductive Technology Accreditation Committee (RTAC) of the Fertility Society of Australia also issues a Code of Practice for accreditation of all IVF clinics.

4.2 The chapter evaluates the adequacy and effectiveness of the current legislation and research guidelines to deal with current and likely future technological processes with human cloning projects.

4.3 The definition of cloning in the three States which have relevant legislation is not consistent.[60] The importance of clearly defining this term will be of great importance in ensuring adequate regulation of this expanding area of science.

Embryo Experimentation

4.4 Some of the work in cloning research may involve human embryos. In this case, the current legislation and ethical guidelines on human embryo experimentation will apply directly to such research proposals.

4.5 State and Territory governments established Committees of Inquiry which produced a succession of Australian reports on IVF[61] during the 1980s. These reports also dealt with the difficult and controversial issue of embryo experimentation. There continues

---

[59] National Health and Medical Research Council, Ethical guidelines on assisted reproductive technology (AGPS 1996); National Health and Medical Research Council, Statement on Human Experimentation 1992 (AGPS), National Health and Medical Research Council, Statement on Human Experimentation Supplementary Note 7 – Somatic Gene Cell Therapy (AGPS)

[60] The Victorian *Infertility Treatment Act 1995* defines the verb "to clone" as meaning to form, outside the human body, a human embryo that is genetically identical to another human embryo or person. The Western Australian *Human Reproductive Technology Act 1991* uses "cloning" to mean the use of reproductive technology for the purpose of producing, from one original, a duplicate or descendant that is, or duplicates or descendants that are, genetically identical, live born and viable. The South Australian Code of Ethical Research Practice defines cloning as "any procedure directed at producing two or more genetically identical embryos from the division of one embryo." This appears to cover embryo splitting but may not cover nuclear transfer.

[61] Victoria produced from 1982-84 three separate reports - Interim Report, of the Committee to Consider the Social Ethical and Legal Issues arising from IVF; Report on Donor Gametes in IVF; Report on Disposition on Embryos produced by IVF; South Australia produced in 1984 a Report of the Working Party on IVF and AID; Queensland in mid 1984 produced a Report of the Special Committee appointed by the Queensland Government to enquire into the Laws relating to AID, IVF and Related Matters; Western Australia produced in August 1984 an Interim Report of the IVF Ethics Committee of WA and a final report in 1986; Tasmania produced in December 1984 and June 1985 respectively an Interim and Final Report of the Committee to Investigate Artificial Conception and Related Matters; the NSW Law Reform Commission produced a Report on Human Artificial Insemination in 1986. Other reports of interest are the Family Law Council of Australia Report entitled Creating Children: A Uniform Approach to the Law and Practice of Reproductive Technology in Australia , the Commonwealth Senate Select Committee on Human Embryo Experimentation in Australia., the NSW Law Reform Commission's In Vitro Fertilisation (NSWLRC58, 1988) and Surrogate Motherhood (NSWLRC 60,1988).

to be a tension between views that the embryo is, if not a human being, certainly deserving of respect, and that some experimentation ought to be allowed to uncover information relevant for the purposes of: (a) improving IVF techniques; (b) understanding male infertility; (c) understanding chromosomal abnormalities; (d) understanding gene defects; and (e) improving contraception.

4.6 Most reports recommended that no experimentation could be carried out either on embryos produced specifically for research or on embryos excess to IVF requirements.[62]

Victoria

4.7 Victoria was the first state and the first jurisdiction in the world to introduce legislation to regulate infertility treatment. Legislation was later introduced in both Western Australia and South Australia.

4.8 The Victorian *Infertility Treatment Act 1995* explicitly prohibits certain research which involves the "formation or use of a zygote if the research proposed that the zygote continue to develop to syngamy"[63] Amongst other prohibited practices is altering the genetic constitution of a gamete intended for use in a fertilisation procedure.[64]

Western Australia

4.9 The Western Australian *Human Reproductive Technology Act 1991* contains a list of offences which include conducting unapproved research or diagnostic procedures with an egg in the process of fertilisation or an embryo, and maintaining an embryo outside the body of a woman after fourteen days from the time of mixing of the gametes.

4.10 Ministerial Directions under the *Human Reproductive Technology Act* 1991 (WA) include regulations which would apply if research involving human cloning were to be carried out.[65] Where approval is sought for any research or diagnostic procedure to be carried out involving an embryo, the intention must be that the procedure will be therapeutic and unlikely to have any detrimental effects.[66]

South Australia

4.11 The *Reproductive Technology Act 1988*, together with the *Reproductive Technology (Code of Ethical Clinical Practice) Regulations* and the *Reproductive Technology (Code of Ethical Research Practice) Regulations*, prohibit, except in accordance with a licence, experimenting with "human reproductive material" (meaning a human embryo, human semen or a human ovum).

[62] The Victorian Report of Professor Waller recommended limited research be permitted and that this be scrutinised by a standing review and advisory committee.
[63] s26 *Infertility Treatment Act 1995*
[64] s39 *Infertility Treatment Act 1995*
[65] s8(6) *Human Reproductive Technology Act 1991*
[66] s9(4) *Human Reproductive Technology Act 1991*

New South Wales

4.12 In October, 1997, the New South Wales Government issued a discussion paper titled "Review of the Human Tissue Act 1983". In the Foreword to this paper, the New South Wales Minister for Health, the Hon. Dr Andrew Refshauge stated that

> *In response to community concern the Government has decided to introduce a law to ensure that two procedures do not develop in New South Wales. The Government has announced the banning of human cloning and trans-species fertilisation involving human gametes or embryos.*

NHMRC Ethical guidelines on assisted reproductive technology (ART)

4.13 The NHMRC has published specific guidelines dealing with ART which include reference to cloning of human beings. The Ethical Guidelines were tabled in Parliament prior to their release in 1996. These guidelines were accompanied by a recommendation that they form a basis for complementary legislation in the States and Territories which had not yet introduced legislation.

4.14 The NHMRC Act authorises the Council to issue guidelines for the conduct of health research and of other purposes related to health. Although infringement of their provisions is not a legal offence, sanctions for infringement usually involve loss of access to research funds from the fund managed and administered by the Council or publication of the names of infringers in Parliament. The guidelines are regarded as national standards of acceptable practice.

4.15 The NHMRC Ethical Guidelines include a number of guidelines relating to embryo experimentation. A practical requirement of note is that "the recognition that any experimentation and research involved in these technologies should be limited in ways which reflect the human nature of the embryo, acknowledging that there is a diversity of views on what constitutes the moral status of a human embryo, particularly in its early stages of development".[67]

4.16 The NHMRC Ethical Guidelines contain restrictions on research relevant and specifically prohibit certain practices.[68]

Comment

4.17 In Australia, substantial limits are placed on research involving embryos. Statutory approval for embryo experimentation is required in three States. The effect of the *NHMRC Statement on Human Experimentation* and the specific NHMRC Ethical Guidelines which deal with embryo experimentation allow research in this area only in exceptional circumstances. In the other States and Territories an institutional ethics

[67] National Health and Medical Research Council, *Ethical guidelines on assisted reproductive technology*, Introduction, p.1 (AGPS, 1996)

[68] National Health and Medical Research Council, *Ethical guidelines on assisted reproductive technology*, paragraphs 6.1 – 6.4 and Section 11 (AGPS, 1996)

committee (IEC) is required to grant approval for such research in accordance with *the NHMRC Ethical guidelines on assisted reproductive technology*.

Assisting in Reproductive Technology Programs

4.18 Cloning techniques of nuclear transfer or embryo splitting could have applications in assisted reproductive programs. One commentator[69] has noted that the nuclear transfer process may have applications in assisted reproductive programs to overcome male infertility problems. An infertile husband could benefit from the asexual nuclear transfer process by contributing his genetic material to the enucleated cell of his wife. Applications of cloning techniques could be used to assist in ART by the splitting of embryos, so increasing the number of embryos for later transfer, facilitating fertilisation in women over 40 (by cloning of the mitochondrial or gene set (cytoplasm replacement)), or replacing defective mitochondrial genes that cause disease.

4.19 If any of these procedures were to be undertaken in ART programs, statutory and/or ethical committee clearance would be required. Assisted reproductive technology is regulated by specific legislation in three States[70] There is a system of self-regulation and accreditation comprising the RTAC and its Code of Practice for units using IVF and related reproductive technologies, with RTAC setting professional and laboratory standards for clinical practice under this system of accreditation.

Status Of Children Legislation

4.20 The status of any child born in an ART program is addressed in State and Territory legislation. This legislation[71] was introduced so that any person donating *gametes* to another person in an assisted reproductive process was not the parent at law of that child. In essence this legislation established the principle that the recipient social parent, rather than the biological parent, assumed all responsibilities at law for that child. In addition, the legislation also established that the person contributing the gametes did not assume any parenting responsibilities at law under such an arrangement.

4.21 This legislation rests on the donation of *gametes* rather than the contribution of *genetic material*. In a scenario where an infertile husband contributes his own genetic material by way of nuclear transfer, the genetic as well as legal relationship is to the husband. On the other hand, were the genetic material to be contributed by a person other than the husband, current legislation may not apply.[72]

---

[69] Robertson JA, Liberty, Identity and Human Cloning, *Texas Law Review* (76(6):1371, 1998)

[70] Victorian *Infertility Treatment Act(1995)*, South Australian *Reproductive Technology Act (1988)* and the Western Australian *Human Reproductive Technology Act (1993)*.

[71] *Artificial Conception Act* 1984 (NSW); *Status of Children Act* 1974 (Vic); *Family Relationships Act* 1975 (SA); *Status of Children Act* 1974 (Tas); *Status of Children Act* 1978 (Qld); *Artificial Conception Act* 1985 (WA); *Artificial Conception Act* 1985 (ACT); *Status of Children Act* 1978 (NT); *Family Law Act* 1975 (Cth).

[72] The current Australian Status of Children legislation establishes that a person donating *gametes* is not the parent at law. It is not clear what the position is in relation to donated genetic material *per se*. The definition sections in the various *Status of Children Acts* in the different States and Territories could be amended to accommodate the donation of genetic material for the purposes of an ART program (should such procedures be considered ethically acceptable).

Replacing Human Tissue and Organs

4.22 In Chapter 2 there was discussion about early stage research into the development of cell lines from embryonic stem cells. This research may illuminate understanding of the programming and reprogramming of cell lines. Understanding of the process of differentiation and dedifferentiation could be the key to provide an unlimited source of therapeutic cells from which transplantable tissue and organs might result.

Human Tissue Legislation

4.23 All Australian States have enacted legislation regulating the donation and transplantation of human tissue.[73] The definition of "tissue" is not identical, but in NSW includes "an organ, or part, of a human body and a substance extracted from, or from a part of, a human body". In essence, this legislation requires the consent of the parties involved for the donation and for the acceptance of the human tissue in a transplantation procedure.

4.24 Current human tissue legislation may apply to some aspects of proposed cloning techniques. Where a cloning technique uses material from one body for transplantation to another or for research or other purposes, the consent provisions of the human tissue legislation would apply.

Cloning an Individual Human Being – Prohibitions in Australia

State Legislation

Victoria

4.25 The Victorian *Infertility Treatment Act 1995* deals specifically with cloning and defines it as the formation "outside the human body" of "a human embryo that is genetically identical to another human embryo or person". The Act prohibits a person from carrying out or attempting to carry out cloning. The Victorian Act contains prohibitions on destructive research on embryos. There are several clauses with a very direct bearing upon cloning.[74]

Western Australia

4.26 In Western Australia, the *Human Reproductive Technology Act 1991* establishes a regulatory structure and Code or Practice. The Act itself contains a list of offences including any procedure directed at human cloning or producing a chimaera.[75]

---

[73] *Transplantation and Anatomy Act* 1978 ss. 6-10 ACT; *Human Tissue Act* 1983, ss. 6-9 NSW; *Human Tissue Transplant Act*, ss. 6-10, NT; *Transplantation and Anatomy Act* 1979, ss. 8-12, Qld.; *Transplantation and Anatomy Act* 1983, s.7-10, SA; *Human Tissue Act* 1985 ss. 5-9, Tas; *Human Tissue Act* 1982, ss. 5-12, Vic.; *Human Tissue and Transplantation Act* 1982 ss. 6-9, WA. On the ethical guidelines of tissue donation see AHEC Series of Papers Donating Organs After Death; Ethical Issues in Donation of Organs and Tissue of Living Donors; and Certifying Death: The Brain Function Criterion.

[74] *Infertility Treatment Act 1995*, sections 24 and 25

[75] "Cloning" is defined as the use of reproductive technology for the purpose of producing, from one original, a duplicate or descendants that are, or duplicates or descendants that are, genetically identical live born and viable.

South Australia

4.27 The South Australian Code of Ethical Research Practice also contains a list of prohibitions which include: cloning[76]; altering the genetic structure of a cell while that cell forms part of an embryo or an ovum in the process of fertilisation; replacing the nucleus of a cell of an embryo or of an ovum in the process of fertilisation with any other nucleus; and placing reproductive material in the body of an animal.[77]

4.28 The procedure of nuclear transfer which does not involve human semen may not be regulated by the Act or the South Australian Code of Ethical Clinical Practice. The Code of Ethical Clinical Practice does not contain a definition of the term "cloning".

NHMRC Ethical guidelines on assisted reproductive technology

4.29 The NHMRC Ethical Guidelines list a number of practices which are considered to be ethically unacceptable and to be prohibited. These include experimentation with the intent to produce two or more genetically identical individuals, including development of human embryonic stem cell lines with the aim of producing a clone of individuals.

4.30 Supplementary Note 7[78] to the NHMRC *Statement on Human Experimentation* clearly states that the introduction of pieces of DNA or RNA into germ (reproductive) cells or fertilised ova is not acceptable, because there is insufficient knowledge about the potential consequences, hazards, and effects on future generations.

4.31 Specific accreditation standards have been formulated by the RTAC and the Fertility Society of Australia has included in its Code of Practice a specific prohibition on nuclear transfer.

Comment

4.32 Embryo splitting and nuclear transfer for the specific purpose of cloning an identical human being is either prohibited or against the intention of the regulatory framework established in Victoria, Western Australia, South Australia and the NHMRC Ethical Guidelines. Production of embryonic stem cell (ES cell) lines is contravened by the Victorian and Western Australian Acts and NHMRC Ethical Guidelines.

Common Law

4.33 There is a general principle that contracts whose formation or performance is contrary to public policy are not enforceable in a court. In determining whether contracts are contrary to public policy, courts can have regard to relevant legislation. Thus, where

---

"Chimaera" is defined as a single living organism which has a mixed genetic origin as a consequence of combining cells derived from different human embryos or human and other species.

[76] "Cloning" is defined as any procedure directed at producing two or more genetically identical embryos from the division of one embryo (R2). It should be noted that this definition does not extend to the procedure of nuclear transfer and is probably only limited to embryo splitting.

[77] Reproductive material is defined as human reproductive material.

[78] NHMRC, Supplementary Notes 7 (1992) of the *NHMRC Statement on Human Experimentation and Supplementary Notes*, AGPS, 1992.

statutes prohibit cloning, there would be grounds for concluding that a contract to provide tissue for the purpose of cloning an individual human being was contrary to public policy and thus unenforceable. Unenforceability alone does not, of course, provide a ground for prohibition of such contracts and does not mean that the parties by their contract have acted illegally.

Privately Funded Institutions

4.34 A concern at this stage is whether a private, rather than publicly funded, organisation in a State or Territory other than Victoria, Western Australia or South Australia might consider a venture in cloning of human being or cloning of human *parts* without the approval of an IEC under NHMRC guidelines. Currently, the NHMRC guidelines are only enforceable against institutions receiving NHMRC funding. The possibility exists that a private institution could decide to undertake such work. Without legislation the NHMRC cannot stop private institutions conducting such work.

CHAPTER 5 - INTERNATIONAL LEGISLATION AND GUIDELINES RELEVANT TO CLONING IN EXISTENCE AT NOVEMBER 1998

This chapter considers overseas regulations which have been introduced as a response to widespread and unequivocal international concern about the possible applications of cloning processes to produce an identical human being.

The United Nations

5.1 The United Nations Economic, Scientific and Cultural Organisation (UNESCO) has concluded the *Universal Declaration on the Human Genome and Human Rights*[79]. This Declaration has received widespread support and was adopted unanimously and on November 11 1997, by UNESCO's 186 member States, including Australia. Australia regards the Declaration as acceptable and has supported the continued existence of the International Bioethics Committee as an expert group to consider the monitoring of the implementation of the Declaration.

5.2 The key operative provision in relation to cloning is Article 11 of the Declaration which states that:

> *Practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted. States and competent international organisations are invited to co-operate in identifying such practices and in determining, nationally or internationally, appropriate measures to be taken to ensure that the principles set out in this Declaration are respected.*

5.3 Even though this Declaration does not include any mandatory provisions requiring States either to introduce domestic legislation or enforce this Article, the terms of the Declaration establish standards which should be observed by governments, scientific organisations, institutions and researchers. International treaties and declarations are also considered by courts of law as creating standards to be applied when interpreting domestic Australian legislation.

Council of Europe

5.4 The Council of Europe has developed international standards to guide the domestic legislation of member States. None of these instruments impose binding legal obligations upon Australia. Of importance in this area is the Council of Europe *Convention for the Protection of Human Rights and Dignity with Regard to the Application of Biology and Medicine* and the *Additional Protocol on Human Cloning*. This additional protocol was based substantially on the wording of the cloning ban

[79] Australia has been an active participant in the development of this Declaration. Australian High Court Judge, Justice Michael Kirby is a member of UNESCO's International Bioethics Committee which formulated the draft Declaration in December 1996.

included in the Report to the European Commission entitled *Ethical aspects of cloning techniques*[80] which was handed down on 28 May 1997.

5.5 The Convention provides a broad framework of principles to guide the development of national legislation regulating biology and medicine. An Additional Protocol to the Convention on Human Rights and Biomedicine on the Prohibition of Cloning Human Beings, was adopted by the Council of Europe on 12 January 1998.

5.6 The Protocol is limited to a ban on the cloning of human beings by embryo splitting or nuclear transfer. It does not prohibit the cloning of cells as a technique per se and it does not deal with the use of embryonic stem cells.

5.7 The Convention and the Protocol, may be signed by States that are not members of the Council of Europe but which have participated in its elaboration. Australia participated in the development of the Protocol and has been invited by the Council of Europe to sign the Convention and Protocol.

The World Health Organisation

5.8 The World Health Organization (WHO) passed a resolution in 1997 affirming that the "use of cloning for the replication of human individuals is ethically unacceptable and contrary to human integrity and morality".

United Kingdom

5.9 In December 1998, the Human Genetics Advisory Commission and the Human Fertilisation and Embryology Authority (HFEA) published a joint report entitled "Cloning Issues in Reproduction, Science and Medicine". The overwhelming majority of submissions to the consultation paper rejected the application of cloning techniques to the creation of genetically identical individuals.

5.10 The possibility of conducting cloning of human beings in the United Kingdom is effectively prohibited by the current provisions of HFEA Act. The HFEA Act does not expressly prohibit embryo splitting or nuclear replacement of eggs, however since both techniques involve the use or creation of embryos outside the body a licence is required. In 1997, the HFEA announced a policy not to issue licences for any procedures involving embryo splitting or nuclear transfer to any IVF practice.[81]

5.11 The Royal Society in the United Kingdom has also made a learned statement which also declares morally and ethically unacceptable any procedure involving reproductive cloning of humans.[82]

[80] Group of Advisers on Ethical Implications of Biotechnology (GAEIB) to the European Commission, Ethical aspects of cloning techniques (1998)
[81] The Human Fertilisation and Embryology Authority (HFEA) has comprehensive authority and jurisdiction over all clinics and laboratories dealing with gametes or embryos whether these clinics and laboratories are in either the private or public sector.
[82] The Royal Society: The UK Academy of Science, Whither Cloning? (13 Feb 1998)

5.12 At the time of presentation of this report a joint committee of the Human Genetics Advisory Commission and the Human Fertilisation and Embryology Authority (HFEA) published its report entitled *Cloning Issues in Reproduction Science and Medicine* December 1998. This Report proposed, *inter alia* a statutory ban on the intentional reproductive cloning of human beings but supported the issue of licences by the HFEA for the application of cloning research on human *parts* to investigate potential benefits in developing methods of therapy for mitochondrial diseases and developing methods of therapy for diseased or damaged tissues or organs.

United States of America

5.13 In March 1997, the President of the United States directed that no Federal funds should be allocated to any research procedure for the cloning of human beings. In addition, the President requested that the National Bioethics Advisory Commission (NBAC) examine and report within 90 days on the ethical, legal and social implications of cloning through somatic cell nuclear transfer techniques. In its report[83] the NBAC noted that there were no Federal regulations prohibiting the use of private funds for the purpose of cloning of human beings. The report is restricted to the issue of somatic cell nuclear transfer, although the NBAC recognised that the use of any other technique to create a child genetically identical to an existing or previously existing individual would raise the same ethical concerns.

5.14 The NBAC made a number of recommendations including the introduction of federal legislation to prohibit anyone from attempting to create a child through somatic cell nuclear transfer cloning on the grounds that it is morally unacceptable because current scientific information indicates that the technique is not safe to use in humans at this point in time. The Commission did not close off the possibility of regulating rather than banning the use of such procedures in the future. The NBAC suggested further careful consideration of the issue and recommended a moratorium for a 5 year period on the basis that "current scientific information indicates that this technique is not safe to use in humans at this point". Clearly, the issue of safety rather than ethical judgment was uppermost in the formulation of this recommendation.

5.15 It should be noted that the position adopted by the NBAC is not consistent with the UNESCO Declaration which expressly prohibits human cloning.

5.16 On 9 June 1997, the President introduced into the US Congress *The Cloning Prohibition Bill 1997* which proposed a review of the prohibition of human cloning by the NBAC five years after passing of the Act. This Bill prohibits the cloning of humans or the conduct of research for the purpose of cloning a human being or creating a human embryo and also prohibits any Federal funds being used for any such research.

[83] National Bioethics Advisory Commission, Cloning Human Beings: Report and Recommendations of the National Bioethics Advisory Commission (June 1997)

Canada

5.17 In 1993, a Royal Commission on New Reproductive Technologies was established to conduct a comprehensive inquiry into the use of existing and newly developing reproductive technologies. The ensuing report does not examine in detail the issue of human cloning but does cover the issue of the use of embryos for research purposes, noting that some forms of embryo research are clearly unacceptable, including human cloning.

5.18 In July 1995, the Canadian Federal Government imposed a voluntary moratorium prohibiting various reproductive techniques which included human embryo cloning. A Bill has been introduced aimed at amending the Canadian Criminal Code to make the knowing use of techniques to achieve human cloning a criminal offence. The Bill had its first reading in the House of Commons on 9 October 1997.

Other Countries

5.19 The Human Genetics Advisory Commission, UK paper provides a brief list of the countries which implicitly or explicitly prohibit human cloning. These are Denmark, Germany, Norway, Slovakia, Spain, Sweden and Switzerland. Greece, Ireland and the Netherlands do not currently have legislation relating to cloning.[84]

[84] Denmark: *Act No. 503 on a Scientific Ethical Committee System and the Handling of Biomedical Research Projects (1992); Act No. 460 on Medically Assisted Procreation in connection with medical treatment, diagnosis and research (1977);* Germany: *Federal Embryo Protection Act 1990;* Norway: *Law No. 56 on the medical use of biotechnology 1994;* Slovakia: *1994 Health Care Law;* Spain: *Law No. 35/1988 on Assisted Reproduction Procedures;* Sweden: *Law No. 115 14 March 1991;* Switzerland: *Federal Constitution*.

CHAPTER 6 – RECOMMENDATIONS AND RESOLUTIONS

The following recommendations and resolutions are made in respect of an appropriate regulatory framework and in relation to allied matters.

Recommendations to the Commonwealth Minister for Health and Aged Care

Recommendation 1

The Commonwealth Government, through the Minister for Health and Aged Care, should reaffirm its support for the UNESCO *Declaration on the Human Genome and Human Rights*, in particular Article 11, which states that:

> *Practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted. States and competent international organisations are invited to cooperate in identifying such practices and in determining, nationally or internationally, appropriate measures to be taken to ensure that the principles set out in this Declaration are respected.*

Recommendation 2

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*.

Recommendation 3

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*.

Recommendation 4

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.

Resolutions of the Australian Health Ethics Committee pending State and Territory Legislation

Resolution 1

The AHEC proposes that, until legislation is introduced in the remaining States and Territories, the AHEC will collect information from institutional ethics committees (IECs) in these States and Territories on IEC research approvals of projects involving the application of current cloning techniques to human embryos. This information will be obtained in the course of the IEC annual compliance reporting system that is currently in place.

Resolution 2

The AHEC proposes that, until legislation is introduced in the remaining States and Territories, the NHMRC should consider the establishment of an expert advisory committee to assist IECs which seek advice on the scientific aspects of research projects involving the application of current cloning techniques to human embryos.

APPENDIX 1

PRIMATE RESOURCES FOR RESEARCH IN EMBRYOLOGY AND DEVELOPMENT IN AUSTRALIA

A1 Consideration should be given to establishing a primate research facility in Australia to carry out a small program related to cloning and its associated technologies (stem cell biology, cell lineage, twinning) and the associated disciplines (reproductive biology, gamete biology, endocrinology, immunology, primate management and veterinary care).[85] The advantages of building up Australian capacity in this area are as follows

- the safety issues which have been highlighted in a number of the reports[86] could be subject to Australian scientific testing
- the feasibility of embryonic stem cell and cell lineage research could be tested
- Australian researchers would be able to carry out basic research and participate in international programs
- necessary expertise and knowledge could be developed within Australia, and
- overseas results could be scrutinised and tested.

A2 The existing primate resources in Australia would have to be expanded to enable Australian researchers to undertake effective work in the area. This would require an initial decision to develop an Australian primate research program including choices as to species to be used. It is estimated that a maintenance budget of $2.5-3 million per year would be required. Capital expenditure would approximate $1 million for purchase of animal breeding stock and up to $4 million for a suitable facility, depending on its location.

Primate Resources in Australia or Abroad

A3 Primate resources in Australia of any significant size include the National Breeding Colonies for marmoset monkeys (sixty pairs – Monash University), macaques (sixty-five births per year – University of Melbourne, Werribee) and baboons (a few animals – Campbelltown). The marmoset breeding group is being moved from CSIRO Adelaide and will not be productive for another one to two years and is already well over-subscribed. The macaque group is also already over-subscribed. The baboons are largely utilised for research in renal and diabetic work at Prince Alfred's in Sydney. There are small colonies of marmosets and macaques in other universities, including forty marmosets at the Psychology Department of the University of New England; and similar numbers of marmosets at the Royal Women's Hospital in Melbourne and at the University of Adelaide. The NHMRC has taken overall

[85] The AHEC acknowledges the helpful summary information provided by Professor John Hearn, Research School of Biological Sciences, ANU, which was most helpful in the formulation of this section.

[86] See particularly *National Bioethics Advisory Commission*, Cloning Human Beings Rockville, Maryland, USA, June 1997 at 65-66

responsibility for primate resources. Advice received by the AHEC suggests that there are inadequate primate resources for an effective research program.

A4 The European Union has assessed primate resources and indicated that they are "a crisis for biomedical research", although in fact there are numerous laboratories throughout Europe and the German Primate Centre in Gottingen is highly developed with large numbers of at least six species. In Britain the large research groups are in Edinburgh (MRC), Oxford and Cambridge. In the United States the NIH supports the National Network of seven regional primate research centres with a block grant budget of approximately $50 million per year, which attracts about twice as much in external research grants. This program supports about 15,000 animals of seventeen species. Two of these centres, Oregon and California have large research groups in reproductive biology, the former with a strong emphasis in gamete biology and embryology, including cloning and twinning. The US NIH program now breeds 85% of its replacement stock, importing the rest for short-term work such as research in AIDS.

A5 Other international resources include substantial colonies in several developing countries. There are five to six well-run research colonies of rhesus monkeys in India; cynomolgus in Thailand and rhesus in China. There are colonies of baboons and other African species at the Institute of Primate Research in Kenya and several smaller colonies of marmoset monkeys in Brazil. Indonesia has a substantial primate centre with cynomolgus and pigtail monkeys at Bogor and there are some large commercial colonies of cynomolgus in the Philippines.

Developing an Australian Program

A6 The NHMRC has responsibility for primate resources in Australia. The NHMRC should therefore be responsible for increasing and developing the Australian capability. This would require a number of key decisions to be made about the species of animals to be acquired, housing, management and welfare of these animals, and any increase in animal numbers. Further consideration should also be given to the need for improvement in capabilities of laboratory facilities, infrastructure and networking of existing labs, and the appropriate budget allocation for the purchase and maintenance of these animals.

Alternative Strategy

A7 If Australia were not to develop its own primate resources capacity to enable Australian researchers to carry out this type of work, the NHMRC could be invited to develop and support travel and research grants for Australian researchers who could travel to use facilities and laboratories overseas.

APPENDIX 2

ACKNOWLEDGEMENTS

A1 In response to a request from to the Minister for Health and Aged Care, the Hon. Dr Michael Wooldridge MP, the Australian Health Ethics Committee (AHEC) of the NHMRC convened a Working Group to address the scientific, ethical and legal considerations in pursuit of cloning of human beings.

A2 The working group was chaired by the Chairman of the AHEC, Professor Donald Chalmers. The other members of the group were Dr Peter McCullagh, the Hon. Dame Margaret Guilfoyle DBE, Dr Bernadette Tobin and Dr Wesley Whitten. The working group would like to acknowledge and express their appreciation of the assistance provided by Dr Cindy Wong and Ms Kaye Sperling in preparing this report.

A3 The work of the Australian Health Ethics Committee is also acknowledged. This report was approved by the full membership of AHEC.

A4 Listed below are the learned individuals and organisations whose comments on an earlier draft of this report were extremely helpful and to whom the Working Group of the Australian Health Ethics Committee is most grateful. The working group is especially grateful for the assistance provided by the Office of International Law of the Commonwealth Attorney-General's Department, in particular Ms Jane Hearn.

Professor Brian Anderson
Australian Academy of Science

Professor Warwick Anderson
Research Committee of the NHMRC

Dr Gordon Baker
Reproductive Technology Advisory Committee of the Fertility Society of Australia

Dr David Bennett
Australian Academy of the Humanities

Sr Mary Byrne
Plunkett Centre for Ethics in Health Care

Catholic Women's League Australia
Bioethics Working Party

Cardinal Edward Clancy
Archbishop of Sydney

Professor Tony Coady
Australian Academy of the Humanities

Dr Suzanne Cory
Walter & Eliza Institute for Medical Research

Country Women's Association of NSW

Dr Andrew Dutney
South Australian Council on Reproductive Technology

Dr Mervyn Eadie
Ethics Advisory Committee (Qld)

Dr Thomas Faunce
Australian National University

Dr Richard Fisher
Fertility Society of Australia

Dr John Fleming
Southern Cross Bioethics Centre

Rev Dr Norman Ford
Caroline Chisolm Centre for Health Ethics

Professor John Funder
Baker Medical Research Institute

Rev Dr Gerald Gleeson
Catholic Institute of Sydney

Dr Sandra Hacker
Ethics and Public Health Committee of the Australian Medical Association

Ms Jane Hearn
Office of International Law
Attorney-General's Department

Professor John Hearn
Research School of Biological Sciences
Australian National University

Dr Elizabeth Hepburn
Queensland Bioethics Centre

Ms Joan Kennedy
Queensland Health

Assoc Professor Helga Kuhse
Centre for Human Bioethics
Monash University

Dr Diana Lange
Queensland Health

Emeritus Professor JM Little
Centre for Values, Ethics and the Law in Medicine, University of Sydney

Dr Robert Loblay
Ethics Review Committee
Australia
Central Sydney Area Health Service

Dr Colin MacLeod
Royal College of Pathologist of

Dr Warwick Neville
Australian Catholic Bishops Conference

Ms Deidre Parsons
South Australian Council on Reproductive Technology

Dr Martin Pera
Institute of Reproduction and Development
Monash University

Ms Elizabeth Percival
Royal College of Nursing, Australia

Professor Peter Phelan
Committee of Presidents of Medical Colleges

Dr Ric Porter
Fertility Society of Australia

Bishop Patrick Power
Australian Catholic Bishops' Committee for the Family and for Life

Ms Prue Richardson
Australian Research Council Secretariat

Professor Vicki Sara
Australian Research Council

Professor Peter Singer
Centre for Human Bioethics
Monash University

Professor Michael Smith
Australian Academy of the Social Sciences

Dr David Swanton

Dr Ron Trent
Gene Therapy Research Advisory Panel
National Health and Medical Research Council

Dr Alan Trounson
Inst. of Reproduction and Development
Monash University

Dr David Turner
Flinders University of South Australia

Professor Louis Waller AO
Infertility Treatment Authority (Vic)

Dr Ian Walpole
Education Social Issues Committee
Human Genetics Society of Australasia

Ms Sandra Webb
Western Australian Reproductive Technology Council

Professor John White
Australian Academy of Science

Dr Bridget Wilcken
Human Genetics Society of Australasia

Professor Bob Williamson
The Murdoch Institute

APPENDIX 3

GLOSSARY OF TERMS

Androgenesis: the production of male parthenotes.

Asexual reproduction: a reproductive process which is not dependant on the fusion of male and female gametes.

Autosome: any chromosome that is not a sex chromosome and that appears as a homologous pair in the somatic cells. Humans have 22 pairs of autosomes which are involved in transmitting all genetic traits and conditions other than those that are sex-linked.

Blastomere: one of the cells which are first formed at the time of division of the fertilised ovum and which, with further cell divisions, become the constituent cells of the morula.

Blastocyst: a ball of cells with a central, fluid-filled cavity (blastocele) surrounded by two layers of cells. The outer layer (trophoblast) later forms the placenta; the inner layer (embryoblast) later forms the embryo. Implantation of the human embryo in the wall of the uterus usually commences at this stage, on approximately the eighth day after fertilisation.

Cellular cloning: the process by which cells derived from the body ('soma') and 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.

Chimaera: an organism with cells from two or more different zygotes.

Chromosomes: any one of the threadlike structures in the nucleus of a cell that function in the transmission of genetic information A normal human somatic cell contains 46 chromosomes; a normal human gamete cell contains 23 chromosomes.

Cloning: asexual propagation without altering the nuclear genome.

Cumulus cells: cells which surround the developing egg in the ovary and remain attached to it after its release. They represent the female homologue of Sertoli cells.

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

Dedifferentiation: a new concept in mammalian embryology describing the process whereby a fully differentiated cell regains totipotency.

Deoxyribonucleic acid: a large nucleic acid molecule, found principally in the chromosomes of the nucleus of a cell, that is the carrier of genetic information.

Differentiated cell line: a line of cells that is committed to producing one type of cell, eg skin cells.

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 the mitochondrion). DNA carries the instructions 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'.

Ectoderm: That one of the three primary germ layers of the embryo which forms its outer covering.

Embryo: the developing organism from the time of fertilisation until significant cellular differentiation has occurred, when the organism becomes known as a 'fetus'.

Embryoid body: a term used to describe a structure with characteristics resembling embryos.

Embryonic stem cell: an undifferentiated cell which is a precursor to a number of differentiated cell types.

Endoderm: One of the primary germ layers of the embryo which lies deep to the ectoderm. It forms the lining of the primitive gut cavity.

Endometrium: the mucous membrane lining of 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 formation of the zygote.

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

Gamete: a mature male or female germ cell; a sperm or ovum.

Gene: a working length of a chromosome composed of DNA. Each of the body's one hundred thousand genes carries the instructions that allow the cell to make one specific product such as a protein.

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

Genotype: the genetic make up of an individual.

Germ cell: a sexual reproductive cell. All other body cells are known as 'somatic' cells.

Gynogenesis: the production of female parthenotes.

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.

Hermaphrodite: animals which contain both ovarian and testicular tissue so that each gonad may be an ovary or a testis or, more commonly, an ovotestis.

Human reproductive cloning: the creation of human beings genetically identical to one another or to any other human being.

In vitro fertilisation (IVF): a technology by which eggs and sperm are collected and put together to achieve fertilisation outside the body.

Meiosis: the division of a sex cell, as it matures, into two and then four gametes with halving of the chromosome complement.

Mesoderm: One of the primary germ layers of the embryo which lies between ectoderm and endoderm.

Mitochondria: cellular organelles that provide energy to the cell. The mitochondrion contains a small number of genes.

Monozygotic: formed from a single fertilised egg.

Morula: a solid, spheric mass of cells resulting from the cleavage of the fertilised ovum in the early stages of embryonic development. It represents an intermediate stage between the zygote and the blastocyst and consists of blastomeres that are uniform in size, shape and developmental capabilities.

Neuron: the basic nerve cell of the nervous system.

Nuclear replacement: a technique which involves fusing the nucleus from a diploid cell or another egg, with an egg from which the nucleus has been removed. The DNA of the transplanted nucleus thus directs the development of the resulting embryo, or egg.

Nucleus: the cell structure that houses the chromosomes, and thus the genes.

Oocyte: the mature female germ cell; the egg

Parthenote: an individual who has been derived exclusively from a single germ cell, female or male.

Phenotype: the complete observable characteristics of an organism or group, including anatomic, physiologic and biochemical features, as determined by the interaction of both genetic makeup and environmental factors.

Placental mammal: This includes all mammals other than the marsupials and monotremes.

Pluripotent: describes a cell or group of cells that can produce many types of tissues.

Polar body: one of the small cells produced during the two meiotic divisions in the maturation process of female eggs, or ova. It contains a haploid set of chromosomes identical with that of the oocyte produced by the same cell division"

Pronucleus: the nucleus of the ovum or the sperm after fertilisation but before the fusion of the chromosomes has occurred to form the nucleus of the zygote.

RNA: Ribonucleic acid

Sertoli cells: elongated cells within the testicular tubules to which the spermatids become attached and from which they derive nourishment. They are the male homologue of the cumulus cells that nourish ova.

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

Teratoma: a tumour composed of different kinds of tissue, none of which normally occur together or at the site of the tumor. Teratomas are most common in the ovaries or testes.

Tetraploid blastocyst: a blastocyst where each cell has four sets of chromosomes. Such blastocysts are not viable.

Totipotent: describes a cell or structure that can produce all cell types including placentas.

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

Trophoblast: the layer of tissue that forms the wall of the blastocyst in the early stages of embryonic development. It functions in implanting the blastocyst in the uterine wall and in supplying nutrients to the embryo.

Zygote: the single-celled fertilised egg.

APPENDIX 4

SELECTED BIBLIOGRAPHY

This bibliography contains a variety of materials utilised by the drafting group in preparing this report. It is not intended to be a comprehensive list of all published information.

Cloning Technology

Ashworth D, Bishop M, Campbell K, Colman A, Kind A, Schnieke A, Blott S, Griffin H, Haley C, McWhir J and Wilmut I, DNA microsatellite analysis of Dolly, *Nature* (1998, 394: 329)

Bongso A, Fong CY, Ng SC & Ratnam S, Isolation and culture of inner cell mass cells from human blastocysts, *Human Reproduction* (1994, 9(11):2110-2117)

Campbell KHS, McWhir J, Ritchie WA and Wilmut I, Sheep cloned by nuclear transfer from a cultured cell line. *Nature,*(1997, 380, 64-6).

Casey D, Cloning: From DNA Molecules to Dolly, *Human Genome News* (Jan 1998:17)

Cibelli JB, Stice SL, Golueke PJ, Kane JJ, Jerry J, Blackwell C, Ponce de León FA, Robl JM, Cloned Transgenic Calves Produced from Nonquiescent Fetal Fibroblasts, *Science* (22 May 1998:1256-1258)

Doetschman TC, Eistetter H, Katz M, Schmidt W & Kemler R, The *in vitro* development of blastocyst-derived embryonic stem cell lines: formation of visceral yolk sac, blood islands and myocardium. *Journal of Embryology experimentation and Morphology.*, (1985, 87, 27-45).

Editorial, Hawaiian Researchers Produce Three Cloned Mice Generations, *Genetic Engineering News* (Aug 18 1998 (14):1,3,36,52,57)

Eppig JJ, Kozak LP, Eicher EM and Stevens LC, Ovarian teratomas in mice are derived from oocytes that have completed the first meiotic division. *Nature,*(1997, 269, 517-8).

Finley MFA, Kulkarni N and Huettner JE, Synapse formation and establishment of neuronal polarity by P19 embryonic carcinoma cells and embryonic stem cells. *The Journal of Neuroscience,* (1996, 16(3), 1056-65).

Gearhart J, New Potential for Human Embryonic Stem Cells, *Science* (1998, 282(5391):1061)

Gurdon JB, The developmental capacity of nuclei taken from intestinal epithelium cells of feeding tadpoles, *Journal of Embryonal Experimental Morphology* (1962, 10: 622-640))

Gurdon JB, The Control of Gene Expression, Animal Development (1974, Oxford, Clarendon Press)

Gurdon JB, Laskey RA and Reeves OR, The developmental capacity of nuclei transplanted from keratinised skin cells of adult frogs, *Journal of Embryonal Experimental Morphology* (10: 93-112, 1975)

Klotzko AJ, Voices from Roslin: The Creators of Dolly Discuss Science, Ethics, and Social Responsibility, *CQ: Cambridge Quarterly of Healthcare Ethics* (7(2):122-140, Spring 1998)

Martin GR and Evans MJ, Differentiation of clonal lines of teratocarcinoma cells: Formation of embryoid bodies *in vitro*. *Proceedings of the National Academy of Sciences. USA.*, (1975, 72(4), 1441-5).

Martin GR, Evans MJ, Multiple differentiation of clonal teratocarcinoma stem cells following embryoid body formation in vitro. *Cell*, (1975, 6, 467-74).

Martin GR, Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. *Proceedings of the National Academy of Science, USA*, (1998 78, 7634-8).

Nagy A, Rossant J, Nagy R, Abramow-Newerly W and Roder JC, Derivation of completely cell culture-derived mice from early-passage embryonic stem cells. *Proceedings of the National Academy of Sciences USA.*,(1993, 90, 8424-8).

Peyron A, Faits nouveaux relatifs à l'origine et à l'histogénèse des embryomes. *Bulletin Association francais étude cancer*, (1939, 28, 658-81).

Regalado A, The Troubled Hunt for the Ultimate Cell,, *Technology Review* (July/Aug 1998: 34-36)

Robertson JA, Human Cloning and the Challenge of Regulation, *New England Journal of Medicine* (9 July 1998, 339(2))

The Royal Society: The UK Academy of Science, Whither Cloning? (13 Feb 1998)
Shamblott MJ, Axelman J, Wang S, Bugg EM, Littlefield JW, Donovan PJ, Blumenthal PD, Huggins GR and Gearhart JD, Derivation of pluripotent stem cells from cultured human primordial germ cells, *Proceedings of the National Academy of Sciences* ((1998 95:13732-13736, 10 Nov 1998)

Shamblott MJ, Axelman J, Wang S, Bugg EM, Littlefield JW, Donovan PJ, Blumenthal PD, Huggins GR and Gearhart JD, Derivation of pluripotent stem cells from cultured human primordial germ cells. *Developmental Biology*, (1998:95 (23), 13726-31).

Shelton JN, Reproductive Technology, Animal Production, *Review of Science, Technology Of. Int. Epiz* (9:825-845, 1990).

Signer EN et al, DNA fingerprinting Dolly, *Nature* (394, 329, 1998)

Solter D, Dolly *is* a clone – and no longer alone, *Nature* (394, 315; 1998)

Stevens LC, Experimental Production of Testicular Teratomas, Mice, *Proceedings of the National Academy of Science USA* (52: 654-661, 1964).

Surani MAH et al, Development of Reconstituted Mouse Eggs Suggests Imprinting of the Genome During Gametogenesis, *Nature* (308: 548-550, 1984).

Tarkowski A K , Experiments on the Development of Isolated Blastomeres of Mouse Eggs, *Nature* (184: 1286-7, 1959)

Teresky AK, Marsden M, Kuff EL & Levine AJ, Morphological criteria for the in vitro differentiation of embryoid bodies produced by a transplantable teratoma of mice. *Journal of Cellular Physiology,* (1974, 84, 319-32).

Thomson JA, Kalishman J, Golos TG, Durning M, Harris CP, Becker RA and Hearn JP, Isolation of a primate embryonic stem cell line. *Proceedings of the National Academy of Sciences USA.*, (1995, 92, 7844-8).

Thomson JA, Istkovic-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS and Jones JM, Embryonic Stem Cell Lines Derived from Human Blastocysts, *Science* (1998, 282 (5391):1154)

Thomson JA and Marshall VS, Primate embryonic stem cells. *Current Topics in Developmental Biology,* 1998, 38, 133-65)

Trounson A and Pera M, Potential benefits of cell cloning for human medicine, *Reproduction, Fertility and Development* (10: 121-5, 1998)

(unknown), Mouse Chimaeras Developed from Fused Eggs, *Nature* (190: 856-860, 1961)

Wade N, Scientists Cultivate Cells at Root of Human Life, *New York Times* (6 Nov 1998:1)

Wakayama T, Perry ACF, Zoccotti M, Johnson RK, Yanagimachi R, Full-term development of mice from enucleated oocytes injected with cumulus cell nuclei, *Nature* (394, 369; 1998)

Wakayama T, Yanagimachi R, The First Polar Body Can Be Used for the Production of Normal Offspring, Mice, *Biology of Reproduction* (59: 100-104, 1998)

Wells DN, Misica PM, Day AM & Tervit HR, Production of cloned lambs from an established embryonic cell line: A comparison between in vivo- and in vitro-matured cytoplasts. *Biology of Reproduction,* (1997, 57, 385-93).

Wilmut I, Schnieke AE, McWhir J, Kind AJ & Campbell KHS, Viable offspring derived from fetal and adult mammalian cells, *Nature* (385:810-13, 27 Feb 1997)

Shorter pieces:

Advanced Cell Technology, Advanced Cell Technology Announces Use of Nuclear Transfer Technology for Successful Generation of Human Embryonic Stem Cells (12 Nov 1998)

Agence France-Presse, Cattle clones could save endangered species, *Sydney Morning Herald* (14 Aug 1998:12)

Associated Press, Chicago physicist says he'll clone himself with wife's help, *The Boston Globe* (7 Sep 1998)

Associated Press, Japan claims a first for cloned calves, *The Sydney Morning Herald* (6 July 1998)

Butler D, Dolly researcher plans further experiments after challenges, *Nature* (391: 825-826, 26 Feb 1998)

Editorial, Hope for world's rarest animals, *New Zealand Herald Daily News* (14 Aug 1998)

Gottlieb S, Scientists cultivate stem cells, the laboratory, *British Medical Journal* (317:1337, 14 Nov 1998)

Human Genetics Advisory Commission, *Cloning Issues, Reproduction, Science and Medicine – Consultation Paper* (15 Jan 1998)

MacQuitty J, The real implications of Dolly, *Nature Biotechnology* (15:254, April 1997)

Nash JM, The Case for Cloning, *Time* (9 Feb 1998:81)

Nature, Cloning: A flock of mice?, Press Release (23 July 1998)

Nature, Cloning: Dolly's DNA profile, Press Release (23 July 1998)

Opinion, Adult cloning marches on, *Nature* (394, 303, 1998)

Stewart C, An udder way of making lambs, *Nature* (385:769-71, 27 Feb 1997)

Yanagimachi T to Whitten WK, personal communication.

Government Policy

Andrews LB, Fullarton JE, Holtzman NA, Motulsky AG, Assessing Genetic Risks. Implications for Health and Social Policy, National Academy Press (Washington DC, 1994: 247-289)

Andrews LB, Mom, Dad, Clone: Implications for Reproductive Privacy, *CQ: Cambridge Quarterly of Healthcare Ethics* (7(2):176-186, Spring 1998)

Australian Health Ethics Committee, *Draft Statement on Ethical Conduct in Research Involving Humans, 1998*

Callahan D, Cloning: Then and Now, *CQ: Cambridge Quarterly of Healthcare Ethics* (7(2):141-144, Spring 1998)

Caton H, Selling Dolly: an ethics hoax, *Bioethics Research Notes* (10(2):13-15, June 1998)

Council of Europe, 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 and Additional Protocol (Jan 1998)

Editorial, Cloning Human Beings: Responding to the National Bioethics Advisory Commission's Report , *Hastings Center Report* (Sep–Oct 1997:6)

House of Commons Science and Technology Committee, The Cloning of Animals from Adult Cells (28 July 1998)

Human Genetics Advisory Commission and the Human Fertilisation and Embryology Authority published its report entitled *Cloning Issues in Reproduction Science and Medicine* December 1998.

Human Genetics Advisory Commission and the Human Fertilitisation and Embryology Authority, Cloning Issues in Reproduction, Science and Medicine (8 Dec 1998)

Messenger A, Cloning - where to now?, *Australian Medicine* (20 April 1998:8-9)

National Bioethics Advisory Commission, Cloning Human Beings: Report and Recommendations of the National Bioethics Advisory Commission (June 1997)

National Bioethics Advisory Commission, Cloning Human Beings: Volume II Report and Recommendations of the National Bioethics Advisory Commission, Commissioned Papers (June 1997)

National Bioethics Advisory Commission, Executive Summary, *Cloning Human Beings: Report and Recommendations of the National Bioethics Advisory Commission* (June 1997:7-9)

Parens E, Tools from and for Democratic Deliberations, *Hastings Center Report* (Sep-Oct 1997:20-22)

Robertson JA, Human Cloning and the Challenge of Regulation, *New England Journal of Medicine* (339(2):1371-1456, 9 July 1998)

Robertson JA, Liberty, Identity and Human Cloning, *Texas Law Review* (1998, 76(6):1371-1456)

The Royal Society: The UK Academy of Science, Whither Cloning? (13 Feb 1998)

Senate Select Committee on the *Human Embryo Experimentation Bill 1985*. Human embryo experimentation in Australia. Parliamentary Paper No 437/1986.

Swanton D, *Human Cloning - a different perspective* (14 May 1998)

United Nations Educational, Scientific and Cultural Organisation, *Universal Declaration of the Human Genome and Human Rights* (3 Dec 1997)

Shorter pieces:

Anastasopoulos C, AMA go-ahead for part cloning, *Australian Doctor* (28 Aug 1998:13)

Australian Medical Association, *Ethics the Key to Cloning Human Genetic Material*, Press Release (12 Aug 1998)

Editorial, Cooling down over cloning, *The Lancet* (351:9097, 17 Jan 1997)

Laurance J, Two generations a chip off the old block, *The Canberra Times* (24 July 1998)

Murray TH, Cloning Now Holds Promise but Raises Issues Concerning the Limitations to Human Power, *Genetic Engineering News* (Feb 1998)

United Nations Educational, Scientific and Cultural Organisation, No to human cloning (Press Kit), 23 June 1998)

Watts J, Japan proposes ban on human cloning, *The Lancet* (352:465, 8 Aug 1998)

Ethical Considerations

Annas GJ, Why We Should Ban Human Cloning, *New England Journal of Medicine* (9 July 1998, 339(2))

Australian Medical Association, Genetic Issues – 1998, Position Statement (July 1998)

Becker GK, Cloning Humans? The Chinese Debate and Why it Matters, *Eubios Journal of Asian and International Bioethics* (7(6):175-177, Nov 1997)

Boyd KM, Little Lamb, Who Made Thee? A Letter from Edinburgh, *CQ: Cambridge Quarterly of Healthcare Ethics* (7(2):199-202, Spring 1998)

Callahan D, Cloning: The Work Not Done, *Hastings Center Report* (Sept-Oct 1997:18-20)

Campbell CS, Prophecy and Policy, *Hastings Center Report* (Sept-Oct 1997:15-17)

Childress JF, The Challenges of Public Ethics: Reflections on NBAC's Report, *Hastings Center Report* (Sep-Oct 1997:9-11)

Cohen S, A House Divided, *The Washington Post* (11 June 1997:W12)

Fitzgerald KT, Human Cloning: Analysis and Evaluation, *CQ: Cambridge Quarterly of Healthcare Ethics* (7(2):218-222, Spring 1998)

Gould SJ, On common ground: individuality, cloning and the discomfitting case of Siamese twins, *The Sciences* (Sep-Oct 1997:14-16)

Group of Advisers on Ethical Implications of Biotechnology (GAEIB) to the European Commission, Ethical aspects of cloning techniques (1998)

Guimerá JFH, Juridico-penal Considerations on Human Embryo Cloning (II), *Law and the Human Genome Review* (2/1995: 89-106)

Harris J, "Goodbye Dolly?" The ethics of human cloning, *Journal of Medical Ethics 1997* (23: 353-360)

Harris J, Cloning and Human Dignity, *CQ: Cambridge Quarterly of Healthcare Ethics* (7(2):163-167, Spring 1998)

Hidalgo SN, Cloning or serial reproduction of human beings, a twenty-first century alternative?, *Law and the Human Genome Review* (No. 4, Jan-June 1996:39-58)

Holm S, A Life, the Shadow: One Reason Why We Should Not Clone Humans, *CQ: Cambridge Quarterly of Healthcare Ethics* (7(2):160-162, Spring 1998)

Kass L, The Wisdom of Repugnance, *The New Republic* (2 June 1997)

Leavitt FJ, The Bioethicist of the Future: Commentary on Pollard and Gilbert, and Melanie Rock, *The Journal of Asian and International Bioethics* (7:133-134, Sep 1997)

Lewontin R, The confusion over cloning , *The New York Review of Books* (16 November 1997)

Little JM, Animal Cloning and the Possibility of Cloning Humans – Science, Law and Ethics, *NSW Judicial Review* (in press)

Nelkin D & Lindee MS, Cloning, the Popular Imagination, *CQ: Cambridge Quarterly of Healthcare Ethics* (7(2):145-149, Spring 1998)

Pollard I, Gilbert S, Bioscience Ethics – A New Conceptual Approach To Modern Ethical Challenges, *The Journal of Asian and International Bioethics* (7:131-133, Sep 1997)

Pollard I, Pollard's Response to Leavitt's Commentary, *The Journal of Asian and International Bioethics* (7:134-135, Sep 1997)

Purdy JS, Dolly and Madison, *The American Prospect* (May-June 1998:88-94)

Raymond J, *Women as Wombs* (Spinifex Press, 1994)

Silver LM, Cloning, Ethics, and Religion, *CQ: Cambridge Quarterly of Healthcare Ethics* (7(2):168-172, Spring 1998)

Singer P, Cloning Humans and Cloning Animals, submission to AHEC (Aug 1998)

Strong C, Cloning and Infertility, *Cambridge Quarterly of Healthcare Ethics* (7:279-293, 1998)

Trounson A and Pera M, Potential benefits of cell cloning for human medicine, *Reproduction, Fertility and Development* (10: 121-5, 1998)

Vatican City, Cloning is 'illicit', *The Catholic Leader* (18 Jan 1998:6)

Wade N, Effort to Make Part-Human, Part-Cow Cells Troubles Clinton, *New York Times* (15 Nov 1998)

Shorter pieces:

Editorial, Cloning: inequality by medical design, *The Catholic Leader* (18 Jan 1998:9)

Hoyle R, Arrogance on human cloning may pose a threat to biotechnology, *Nature Biotechnology* (16:6, Jan 1998)

HUGO Ethics Committee, Statement on cloning (Final Draft), (20 July 1998)

Krauthammer C, Of Headless Mice ... And Men, *Time* (pathfinder.com/time, 19 Jan 1998, 151(2))

Marshall E, Mammalian Cloning Debate Heats Up, *Nature Biotechnology* (15:1733, April 1997)

Marshall E, A Versatile Cell Line Raises Scientific Hopes, Legal Questions, *Science* (1998, 282:5391, 1014)

Nelson JL, Counting Cloned Sheep, *Center View* (6(1):1-2, Sept 1997)

Wade N, Human-Cow Hybrid Cells Are Topic of Ethics Panel, *New York Times* (18 Nov 1998)

Regulatory Framework

Annas GJ, Why We Should Ban Human Cloning, *New England Journal of Medicine* (9 July 1998, 339(2))

Dickens B, Wrongful birth and life, wrongful death before birth, and wrongful law, *Legal Issues, Human Reproduction* (Gower: 80-110)

Guimerá JFH, Juridico-penal Considerations on Human Embryo Cloning (I), *Law and the Human Genome Review* (No 1:49-71, July-Dec 1994)

Hidalgo SN, Cloning or serial reproduction of human beings, a twenty-first century alternative?, *Law and the Human Genome Review* (No 4:39-58, Jan-June 1996)

Human Fertilisation & Embryology Authority, Revised HFEA Code of Practice (Fourth Edition), (London, July 1998)

Japan proposes ban on human cloning, *Lancet* (352:465, 8 Aug 1998)

Kassirer JP, Rosenthal NA, Should Human Cloning Research Be Off Limits?, *New England Journal of Medicine* (26 March 1998, 338(13))

Notes, Human Cloning and Substantive Due Process, *Harvard Law Review* (111(8):2348-2365, June 1998)

Robertson JA, Human Cloning and the Challenge of Regulation, *New England Journal of Medicine* (9 July 1998, 339(2))

Robertson JA, Liberty, Identity and Human Cloning, *Texas Law Review* (1998, 76(6):1371-1456)

Silver LM, Cloning, Ethics, and Religion, *CQ: Cambridge Quarterly of Healthcare Ethics* (7(2):168-172, Spring 1998)

Warnock M, The Regulation of Technology, *CQ: Cambridge Quarterly of Healthcare Ethics* (7(2):173-175, Spring 1998)

Wolf SM, Ban Cloning? Why NBAC is Wrong, *Hastings Center Report* (Sep-Oct 1997:12-15)

Shorter pieces:

AHEC, *Information for IECs: Sheet No. 2* (May 1996)

CCH Australia Ltd, Professional negligence, *CCH Australia Torts Reporter* (Sydney 1998:44492)

Editorial, Legislative Background: Recent Action on Human Cloning, *Congressional Digest* (Feb 1998)

Fleming JG, The Law of Torts, The Law Book Company (1987:154-155)

Trindale FA & Cane P, *The Law of Torts*, Australia, Oxford University Press (Melbourne 1986:319-320)

Watts J, Japan proposes ban on human cloning, *The Lancet* (352:465, 8 Aug 1998)

Related Topics

Australian Medical Association, International survey on human cloning, *Australian Medicine* (16 Nov 1998:12)

Barinaga M, News of the week. New leads to brain neuron regeneraiton. *Science*, (1998, 282, 1018-9).

Bonduelle M, Legein J, Buysse A, van Assche E, Wisanto A, Devroey P, Van Steirtegheim AC and Liebaers I, Prospective follow-up study of 423 children born after intracytoplasmic sperm injection, *Human Reproduction* (11(7):1558-1564, 1996)

Bowen JR, Gibson FL, Leslie GI, Saunders DM, Medical and developmental outcome at 1 year for children conceived by intracytoplasmic sperm injection, *The Lancet* (351:9115, 1988)

Bradley A, Evans M, Kaufman MH & Robertson E, Letters to Nature. Formation of germ-line chimaeras from embryo-derived teratocarcinoma cell lines. *Nature* (1984, 309, 255-6).

Catechism of the Catholic Church (St Paul's, 1994: 552-553, 570-573)

Chapman P, Dolly's team look to make ewe flock with human help, *The West Australian* (17 Sep 1998:14)

Congregation for the Doctrine of the Faith, Instruction on Respect for Human Life, its Origin and on the Dignity of Procreation: Replies to Certain Questions of the Day (Donum Vitae) (St Paul's Publication, 1987)

Cummins JM and Jequier AM, Concerns and recommendations for intracytoplasmic sperm injection (ICSI) treatment, *Human Reproduction* (10(supp 1), 1995)

Evans MJ, Kaufman MH, Establishment in culture of pluripotential cells from mouse embryos. *Nature*, (1981, 292, 154-6).

Friend Bishop, Frontiers of Genetic Research: Science and Religion, *Origins* (24:522-528,1995)

Grabowski JS, Made not begotten: A theological analysis of human cloning, *Homiletic & Pastoral Review* (9:16-21,1998)

Hickman B, Clone plan threatens to create human monsters: scientists, *The Australian* (9 Jan 1998)

Hodgson J, Dolly opens a farm full of possibilities, *Science Biotechnology* (15:306, April 1997)

Hole N, Graham GJ, Menzel U and Ansell JD, A limited temporal window for the derivation of multilineage repopulating hematopoietic progenitors during embryonic stem cell differentiation in vitro. *Blood*, (1996, 88 1266-76).

Human Genetics Advisory Commission, HFEA Update (Aug 1998)

ISLAT Working Group, ART into Science: Regulation of Fertility Techniques, *Science* (281:651-2, 31 July 1998)

Joint Ethico-Medical Committee of the Catholic Union of Great Britain and the Guild of Catholic Doctors, Submission to the Committee on the Ethics of Gene Therapy, *The Linacre Quarterly* (57:14-18,1990)

Keeler Cardinal W, The Problem with Human Cloning, *Origins* (36:597-601,1998)

Kadrey R, Carbon Copy, *Wired Magazine* (www.wired.com, March 1998)

Krob CE, Braun A and Kuhnle U, True Hermaphroditism, Geographical Distribution, Clinical Findings, Chromosomes and Gonadal Histology, *European Journal of Paediatrics* (153:2-10)

Kurinczuk JJ and Bower C, Birth defects, infants conceived by intracytoplasmic sperm injection: an alternative interpretation, *BMJ* (315:1260-66, 15 Nov 1997)

Lerner U, Saxena BN and Diczfalusy E, Extracorporeal perfusion of the human fetus, placenta and foeto-placental unit. *Karolinska Symposia on Research Methods in Reproductive Endocrinolog*y, (1971, 4, 310-25).

Miller LJ and Bloom FE, Publishing Controversial Research, *Science* (282(5391):1045)

Mullen RJ, Whitten WK, The Relationship of Genotype and Degree of Chimerism, Coat Colour to Sex Ratios and Gametogenesis, Chimeric Mice, *Journal of Exploratory Zoology* (278 :165-175, 1971)

National Health and Medical Research Council, *Ethical guidelines on assisted reproductive technology* (AGPS, 1996)

News, Brief, Dolly researchers win grant to continue work ..., *Nature* (394:114, 9 July 1998)

News, Brief, ... as Japanese announce cloned calf twins, *Nature* (394:114, 9 July 1998)

Pence GE et al, To the Editor:, *New England Journal of Medicine* (1998, 339:21, 1558)

Pontifical Academy for Life, Reflexions on Cloning (Vatican City: Libreria Editrice Vaticana, 1997)

Pontifical Council for Pastoral Assistance to Health Care Workers, Charter for Health Care Workers (Vatican City, 1995:23-72)

The Ramsey Colloquium, The Inhuman Use of Human Beings, *First Things* (49:17-21,1995)

Reuters, New heart: grow your own, *The Age* (25 June 1998:A10)

Reynolds BA and Weiss S, Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. *Science*, (1992, 255, 1707-10).

Richards LJ, Kilpatrcik TJ and Bartlett PF, *De novo* generaiton of neuronal cells from the adult mouse brain. *Proceedings of the National Academy of Science USA,* (1992, 89, 8591-5).

Robertson EJ, Evans MJ and Kaufman MH, X-chromosome instability in pluripotential stem cell lines derived from parthenogenetic embryos. *Journal of Embryology experimentation and Morphology*, (1983, 74: 297-309)

Shelton JN, Reproductive technology in animal production. *Review of Science, Technology Office Int.* Epiz. (1990, *9,* 825-45).

Spangrude GJ and Johnson GR, Resting and activated subsets of mouse multipotent haematopoietic stem cells. *Proceedings of the National Academy of Science USA,* (1998, 87, 7433-7).

Spinks P, Cloning cures, *The Age* (17 Sep, 1998:A22)

Steptoe P, p143 in " A matter of life: the story of a medical breakthrough". Edwards R & Steptoe P, Hutchinson, London, 1980.

Stevens LC, Embryology of testicular teratomas in strain 129 mice. *Journal of the National Cancer Institute.,* (1959, 23(6), 1249-95)

Sutherland DE, Pancreas and islet transplantation: now and then. *Transplantation Proceedings,* (1996:28, 2131-3).

Sutherland DE, Gruessner AC and Gruessner RW, Pancreas transplantation: a review. *Transplantation Proceedings,* (1998, 30, 1940-3).

te Velde ER, van Baar AL, van Kooij RJ, Concerns about assisted reproduction, *The Lancet* (351:9115, 23 May 1998)

van Niekirk WA, True Hermaphroditism: Clinical, Morphologic and Cytogenetic Aspects (Harper and Row, New York, 1974).

Wenning GK et.al, Short-and long-term survival and function of unilateral ultrastriatal dopaminergic grafts in Parkinson's disease. *Annals of Neurology,* (1997, 42, 95-107).

Whitten WK, Chromosomal Basis for Hermaphroditism, Mice, *the Developmental Biology of Reproduction* (Academic Press, New York. 1975)

Wilkie T & Graham E, Power without Responsibility: Media Portrayals of Dolly and Science, *CQ: Cambridge Quarterly of Healthcare Ethics* (7(2):150-159, Spring 1998)

Winkel GK and Pedersen RA, Fate of the inner cell mass in mouse embryos as studied by microinjection of lineage tracers. *Developmental Biology,* (1988, 127, 143-56).

Wood C, Artificial Procreation (July 1993)