3

Scientific evidence

INTRODUCTION

3.1 This chapter presents the scientific conclusions from the AHEC report, *Scientific, Ethical and Regulatory Considerations Relevant to Cloning of Human Beings;*[1] the recommendations of the Australian Academy of Science resulting from a review of the status and future directions of cloning and stem cell technologies;[2] the evidence presented to the Committee and the Committee's consideration of the scientific aspects of the inquiry.

The AHEC Report: Scientific Considerations

3.2 The Executive Summary and Recommendations of the AHEC report are at Appendix D. Inevitably new discoveries have resulted in the AHEC report being overtaken to some extent, although it remains a useful background document.[3]

3.3 The AHEC report was published in December 1998. The AHEC working party considered the request from the Commonwealth Minister for Health and Aged Care for advice as to the need for further pronouncement or legislation regarding human cloning. After consultation, there was no support for the application of any technique aimed to intentionally clone whole individual human beings.[4]

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1 Australian Health Ethics Committee of the NHMRC, *Scientific, Ethical and Regulatory Considerations Relevant to Cloning of Human Beings, (*referred to as the AHEC report), 16 December 1998

2 *Human Stem Cell Research*, Australian Academy of Science, 18 April 2001

3 AHEC report, Chapter 1, paragraphs 1.1–1.25; AHEC report, Executive Summary, E1–E9 and Recommendations p.v

4 AHEC report, Executive Summary E2, p.iv

3.4 The AHEC report discussed the support for basic research related to cloning technology in Australia. The report outlined relevant scientific considerations and various techniques for cloning human embryos. It sketched background embryology, technical applicability and feasibility. An outline of the projected benefits of cloning techniques which have the potential for supporting transplantation, tissue and organ repair was given, together with the possible risks of these techniques.[5]

3.5 Ethical issues associated mainly with cloning techniques involving human embryos were identified.[6] These ethical and policy issues form the basis of Chapter 7 in this report. The relevant international and national regulatory frameworks were reviewed, as was the NHMRC *Ethical guidelines on assisted reproductive technology*. The international consensus at that time was that the intentional cloning of humans is unacceptable.[7] This matter is discussed in Chapters 6 and 10 of this report.

The Australian Academy of Science

3.6 The Academy published a position statement *On Human Cloning* in February 1999 and hosted an international forum on *Therapeutic Cloning for Tissue Repair* in September 1999. A statement on *Human Stem Cell Research* was published in April 2001. In the first and third of these documents and in its submission to this inquiry the Academy recommended:

- Reproductive cloning to produce human fetuses is unethical and unsafe and should be prohibited. However, human cells, whether derived from cloning techniques, from embryonic stem cell lines or from primordial germ cells should not be precluded from use in approved research activities in cellular and developmental biology.[8]
- The Minister for Health and Aged Care should encourage informed community debate on therapeutic benefits and risks of development of cloning technologies.[9]
- If Australia is to capitalise on its undoubted strength in medical research, it is important that research in therapeutic cloning should not

5 AHEC report, Chapter 2, paragraphs 2.1- 2.49

6 AHEC report, Chapter 3 paragraphs 3.1-3.33

7 AHEC report, Chapter 4 paragraphs 4.1-4.34, Chapter 5 paragraphs 5.1-5.19

8 *On Human Cloning. A position statement*. February 1999, p.6, *Human Stem Cell Research,* 18 April 2001, p.4, *Therapeutic Cloning for Tissue Repair,* Report from a forum held on 16 September 1999, Australian Academy of Science, *Submissions,* p.S245

9 *On Human Cloning. A position statement*. 4 February 1999, p.6, *Human Stem Cell Research,* 18 April 2001, p.4, *Therapeutic Cloning for Tissue Repair,* Report from a forum held on 16 September 1999, Australian Academy of Science, *Submissions,* p.S245

be inhibited by withholding federal funds or prevented by unduly restrictive legislation.[10]

- It is essential to maintain peer and public scrutiny of all research involving human embryos and human embryonic stem (ES) cells undertaken in Australia. The Academy recommends that a national regulatory two-tier approval process be adopted for research on human embryos and human ES cells. Approval to undertake any research involving human embryos and human ES cell lines would need to be obtained from a duly-constituted institutional ethics committee prior to further assessment by a national panel of experts, established by the National Health and Medical Research Council. Approval would be based on the scientific merits, safety issues and ethical acceptability of the work.[11]

3.7 In its conclusions to *Human Stem Cell Research* the Academy stated:

> The Academy of Science continues to promote public discussion on human stem cell research. Scientists are using terms that are not yet understood by the public; community discussion forces clear definition of terminology but can also find new words that are more broadly understood. Social issues should be canvassed during the debate, such as the potential impact on our view of human-kind as medical technology becomes more manipulative, and on attitudes to and by women as potential donors of eggs and embryos for use in tissue repair.[12]

3.8 Both the AHEC report and the Academy agreed that reproductive cloning of an individual should not be permitted; that research in stem cell biology should be facilitated under agreed guidelines; and that public discussion should be encouraged.

CLONING FOR REPRODUCTIVE PURPOSES

3.9 Scientists from whom the Committee received evidence agreed that there is no medical reason for cloning for reproductive purposes to be attempted in humans. There is no evidence that any Australian scientist approves of the use of cloning technologies to create and bring to birth a live human being, or wishes to be engaged in such work.

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10 *On Human Cloning. A position statement*, Australian Academy of Science, 4 February 1999, p.6, *Human Stem Cell Research*, 18 April 2001, p.4, *Therapeutic Cloning for Tissue Repair*. Report from a Forum held on 16 September 1999; Australian Academy of Science, *Submissions*, p.S245

11 *On Human Cloning. A position statement*, 4 February 1999, p.6; *Human Stem Cell Research*, 18 April 2001, p.4; *Therapeutic Cloning for Tissue Repair*, Report from a Forum held on 16 September 1999; Australian Academy of Science, *Submissions*, p.S245

12 Australian Academy of Science, *Human Stem Cell Research*, 18 April 2001, p.26

3.10 While opinion presented to the Committee was overwhelmingly opposed to cloning for reproductive purposes there were two submissions which argued that a ban on cloning for reproductive purposes is not appropriate because views may change with time.[13] These opinions are noted in Chapter 6.

3.11 Despite statements by scientists such as Dr Arthur Caplan[14] that human cloning is not imminent**,** overseas there appears in some quarters to be a race to clone the first human. Dr Severino Antinori (Italy) and Dr Panayiotis Zavos (USA) state they plan to clone a human within a year or two,[15] and in America a religious group, the Raelians, has announced plans to clone a 10 month old child who died in a hospital accident.[16] These claims have been challenged by many scientists around the world who doubt the ability or capacity of these scientists to produce a human clone with current technology, even if it was ethically acceptable.[17]

3.12 In a recent paper, Dr Jaenisch and Dr Wilmut (who produced Dolly) argue strongly against the cloning of whole human beings. Their arguments are based on the high potential risks of chromosomal damage due to rapid reprogramming[18] of the nucleus over a few hours in nuclear transfer techniques, compared to the months or years taken in natural programming during the development of the sperm or the egg. These risks are becoming evident in many studies of animal cloning. These investigators say:

> We believe attempts to clone human beings at a time when the scientific issues of nuclear cloning have not been clarified are dangerous and irresponsible.[19]

3.13 In the USA, the National Bioethics Advisory Commission reached the same conclusion in 1997:

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13 Professor Felix Beck, *Submissions*, p. S684. Dr Loblay was of the view that at some future time there may be pressure from certain groups to use this technology for reproductive purposes but that 'current community values are such as to make this unacceptable.' Dr Loblay, *Exhibit* 8

14 The Committee on Energy and Commerce: Hearing on Issues Raised by Human Cloning Research (USA) March 2001, http://www.house.gov/commerce/hearings/03282001-141/Caplan211.htm

15 http://news.bbc.co.uk/hi/english/sci/tech/newsid_1209000/1209716.stm, 9 March 2001

16 http://www.washingtonpost.com/wp-dyn/articles/A39671-2000Oct9.html, 10 October 2000

17 http://www.Sunday-times.co.uk/news/pages/sti/2001/03/11stifocnws01003.html 11 March 2001

18 Jaenisch, R., and Wilmut, I., 'Don't Clone Humans!' *Science*, Volume 291, 30 March 2001, p.2552

19 Jaenisch, R., and Wilmut, I., 'Don't Clone Humans!' *Science*, Volume 291, 30 March 2001, p.2552

> At present, the use of this technique to create a child would be a premature experiment that would expose the fetus and the developing child to unacceptable risks.[20]

3.14 The scientific evidence accumulated over the past 5 years only reinforces this position. The reasons for genetic or epigenetic (non genetic, environmental conditions etc) damage to cloned animals are not understood.

Safety— Cloning for Reproductive Purposes

3.15 Almost all submissions to the Committee expressed opposition to cloning for reproductive purposes. Many raised concerns about the associated safety and the serious medical risks. In cloned animals these risks are evident in the many abnormal foetuses formed, with a high proportion of miscarriages and deaths soon after birth. Since there is currently very little support anywhere in the world for cloning for reproductive purposes in human beings, the evidence is presented briefly below with references provided to other relevant submissions and publications.

3.16 In a USA government investigation into Issues Raised by Human Cloning Research, Dr Rudolf Jaenisch explained:

> Most new born clones (animals) are overweight and have an increased and dysfunctional placenta. Those that survive the immediate perinatal period may die within days or weeks of birth with defects such as kidney or brain abnormalities, or with a defective immune system.
>
> The most likely cause of abnormal clone development is faulty reprogramming of the genome. This may lead to abnormal gene expression of any of the 30,000 genes residing in the animal.
>
> The experience with animal cloning allows us to predict with a high degree of confidence that few cloned humans will survive to birth, and of those, the majority will be abnormal.[21]

3.17 Many submissions to this inquiry raised concerns about the high failure rate of cloning attempts and the considerable risks of abnormal development, congenital abnormalities and the effects of somatic cell

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20 National Bioethics Advisory Commission, Executive Summary, *Cloning Human Beings*, http://bioethics.gov/pubs.html p.ii, June 1997

21 The Committee on Energy and Commerce: Hearing on Issues Raised by Human Cloning Research, (USA) 28 March 2001, http://www.house.gov/commerce/hearings/03282001-141/Jaenisch202.htm. See also Gurdon, J.B. and Colman, A., *Nature* Volume 402, 16 December 1999, p.744

mutations and aging DNA on the resulting individual.[22] Some of these fears now appear unlikely, for example, the issue of premature ageing.[23]

3.18 Mr Bill Muehlenberg for the Australian Family Association sums up many of these concerns:

> Any attempts at human cloning (which will be much more complex and difficult than sheep cloning) will undoubtedly involve many failed attempts as well. How many embryos will be lost, how much fetal wastage will occur before we arrive at an acceptable success rate for human cloning.[24]

3.19 In summary, the assessment of all those submitting scientific evidence to the Committee and of international scientific sources is that any attempt to clone a whole human individual is premature and should not be permitted. This concurs with lay opinion presented to the Committee. Ethical issues are considered further in Chapters 5, 6 and 7.

CLONING FOR THERAPEUTIC PURPOSES

3.20 The Committee considered the various forms of cell therapy being derived from research. Inherent in these approaches are those that currently require the formation or use of an embryo and derivation of embryonic stem cells; and those, including aspects of adult stem cell research, that do not require embryos. At present there is not a clear definition of these approaches, or of the full capacities of embryonic and adult stem cells.

3.21 The term 'therapeutic cloning' is used generally to describe three distinct approaches:

- somatic cell nuclear transfer, with stem cells being derived from the blastocyst formed by this procedure;
- embryonic stem cell therapies, resulting from cells derived from an embryo, for example, a surplus embryo from IVF procedures; and

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22 Professor Felix Beck, *Submissions*, p.S683. See also AHEC report Chapter 2, paragraph 2.47; Dr Eloise Piercy, *Submissions*, pp.S582-3; Professor Bob Williamson, *Submissions*, p.S347; Social Responsibility Committee of the Anglican Diocese of Melbourne, *Submissions*, p.S304; Ridley College, *Submissions*, p.S32; Australian Academy of Science *On Human Cloning. A Position Statement*, 4 February 1999, p.9; Dr David Gawler, *Submissions*, p.S626; Natalie Ross-Lapointe, *Submissions*, p.S229; Women's Action Alliance (Victoria) Inc. *Submissions*, p.S782; Neil Ryan, *Submissions*, p.S56

23 Roslin Institute Annual Report 1998-99, p.12. Dolly does not appear to be ageing abnormally

24 The Australian Family Association, *Submissions*, p.S695. See also: Ridley College, *Submissions*, p.S32; Natalie Ross-Lapointe, *Submissions*, p.S229

- adult stem cell therapies where an embryo stage is not involved.

3.22 As set out in Chapter 9 in this report, the reference to 'therapeutic cloning' by AHEC is a reference to limited procedures undertaken on an embryo for the benefit of the embryo. This is distinct from procedures undertaken on an embryo for purposes which may benefit other embryos or persons but which destroy the embryo on which the experiment is undertaken. AHEC refers to these procedures as 'non therapeutic cloning'. Although the expressions 'therapeutic' and 'reproductive' cloning are used commonly, the Committee notes that the term 'therapeutic cloning' can be misleading.[25] For this reason the Committee refers to specific procedures rather than using terminology that is ambiguous.

The Potential Importance To Medicine

3.23 In contrast to the wide consensus against cloning for reproductive purposes expressed by international and national organisations and scientists, there was strong support in the scientific community and elsewhere for cloning for purposes of advancing scientific knowledge, with its potential benefits in many areas of human medicine.

3.24 The 1998 AHEC report commented that 'somatic cell nuclear transfer to a mammalian oocyte is still at an early stage of development'.[26] Notwithstanding the major advances made since then, there is much research to be done before the procedures are either understood or safe for clinical application.

3.25 Many submissions to the Committee recognised the potential value and importance of cloning technologies for clinical medicine, particularly for transplantation medicine and pharmaceutical production. A number of submissions, from scientists and others, hailed the breakthroughs in this field as the most significant and exciting of recent times.

3.26 Professor Marilyn Monk said that:

> The possibility of transplantation of tissue arising from embryonic stem cells in the treatment and cure of disease is the greatest and most exciting medical breakthrough I can envisage in the future.[27]

3.27 This sense of excitement about the new technologies was shared by Dr Karen Milne:

> The scientific advances that have paved the way for new technologies in IVF, cloning, genetic manipulation and transplant

25 See paragraphs 9-11-9.12 of this report

26 AHEC report, Chapter 2, paragraph 2.23

27 Professor Marilyn Monk, *Submissions*, p.S806

> therapies are scientifically exciting and appear to offer life to those who might otherwise not have survived (or existed).[28]

3.28 Similarly, Professor Alan Trounson, speaking of embryonic stem cells, said that 'the derivation of these cells is one of the biggest breakthroughs in human medicine.'[29]

3.29 Professor Robert (Bob) Williamson of the University of Melbourne stated that while recognising that (reproductive) cloning will be medically unsafe,

> … we recognise that there are very great potential benefits in continuing research into ways in which somatic cells from living individuals can become totipotent. These benefits are most clear in the field of transplantation medicine.[30]
>
> …stem cell research is extremely important clinically.[31]

3.30 Dr David Gawler saw as laudable:

> The benefits suggested from the production of human ES cells, including studies of normal and abnormal embryogenesis, aging and cancer, gene discovery, drug testing, a source of transplantable tissue and so on…[32]

3.31 In its submission, St Vincent's Hospital also recognised that these techniques 'seem to hold out great benefits both for our understanding of human biology and our capacity to develop therapies for cancer and other pathologies'.[33]

3.32 The Australian Research Council also recognised the clinical and scientific importance of the cloning procedures:

> There are clinically important reasons for carrying out such procedures, for example, tissue and organ replacement, and therapies involving genetically modified but otherwise genetically identical cells. Scientifically, too, study involving such cells and tissues is important. Specifically, an understanding of mechanisms of cell determination and differentiation, genomic imprinting, and somatic cell aging can all be approached using such procedures.

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28 Dr Karen Milne, *Submissions*, p.S68

29 Professor Alan Trounson, *Transcript*, p.5. See also Professor Julian Savulescu, *Submissions*, p.S650

30 Professor (Robert) Bob Williamson, *Submissions*, p.S347

31 Professor Robert Williamson, *Transcript*, p.8

32 Dr David Gawler, *Submissions*, p.S624. See also Caroline Chisholm Centre for Health Ethics Inc., *Submissions*, p.S491

33 St Vincent's Hospital, *Submissions*, p.S152. See also Dr Paul Jewell, *Submissions*, p.S9; Drs Fleming and Pike, *Submissions*, p.S560

> At present, the use of embryonic stem (ES) cells is the most likely source of such material.[34]

3.33 The Human Genetics Society of Australasia recognised that:

> …the technology used for human reproductive cloning will lead to the development of technologies that have important medical uses. In particular, the creation of totipotent or pluripotent stem cells from somatic cells would markedly simplify transplantation procedures. As transplantation is currently limited by both immune rejection and by availability of tissue this is an important clinical outcome that could bring great benefit.[35]

3.34 The Law Society of NSW submitted:

> …this new technology will have important medical applications. The cloning of human DNA into other species is likely to be of increasing importance for the production of human proteins with pharmaceutical uses such as insulin.[36]

Some Words Of Caution

3.35 Scientific and public submissions agreed on the substantial potential benefits of these technologies. The greatest benefits may be expected in the field of transplantation medicine where the risks of tissue rejection may be avoided by supplying a person with new cells or tissue of exactly their own genetic type. However, the initial enthusiasm for therapeutic cloning is being replaced in recent months by a more cautious view, illustrated by an article in *Nature:*

> So to the casual observer, it may come as a surprise that many experts do not expect therapeutic cloning to have a large clinical impact. Aside from problems with the supply of human egg cells, and ethical objections to any therapy that requires the destruction of human embryos, many researchers have now come to doubt whether therapeutic cloning will ever be efficient enough to be commercially viable. "It would be astronomically expensive," says James Thomson… who led the team that first isolated ES cells from human blastocysts.[37]

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34 Australian Research Council, *Submissions*, p.S225. See also Dr Julian Savulescu, *Submissions*, p.S655

35 Human Genetics Society of Australasia, *Submissions*, p.S508. See also Richard Dewis, *Submissions*, p.S13

36 Law Society of NSW, *Submissions*, pp.S279-80. See also Richard Dewis, *Submissions*, p.S13; Dr Robert Loblay, Central Sydney Area Health Service (RPAH Zone), *Submissions*, p.S677

37 *Nature*, Volume 410, 5 April 2001, p.622

3.36 Mr Robert Klupacs,[38] stated:

> We do, however, support therapeutic cloning under carefully regulated conditions and then only for research purposes, rather than for ongoing clinical therapies.[39]
>
> We do not envisage that it will ever be feasible, or indeed necessary to incorporate therapeutic cloning, which is a very labour intensive and inefficient process, into a routine clinical treatment.[40]

3.37 There are concerns in the recent scientific literature about the possible use of abnormal embryos[41] for the derivation of cell lines, and about inadequate reprogramming of the nucleus during somatic cell nuclear transfer.[42] There are risks that transplanted cells might develop in an uncontrolled way to form the wrong tissue type or cancers in the transplantation sites.[43] Other issues raised included the questionable integration and normal function of transplanted cells in their new site and the possibility that the original disease process would neutralise the transplanted cells.[44] Basic research is necessary before these issues are understood.

3.38 The evidence emphasised the dilemma between the need for painstaking basic and strategic research when the potential medical and health benefits are being assumed as reality and magnified by the press and public. In the race to compete and develop new therapeutic approaches to major medical problems, several scientists and others underlined the need to proceed with rigorous scientific method and clinical trial procedures.[45] Further pressure for immediate results comes from industry, especially in the USA, where there is no restriction on investment and research in the

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38 Mr Robert Klupacs is General Manager and Chief Executive Officer, ES Cell International Pte Ltd

39 Mr Robert Klupacs, *Submissions*, p.S892

40 Mr Robert Klupacs, *Submissions,* p.S893

41 Professor Robert Norman emphasised that in his opinion, the majority of embryos derived from IVF are genetically normal. Professor Robert Norman, *Transcript*, p.104, Dr John Smeaton, *Transcript*, pp.160- 161

42 Jaenisch, R., and Wilmut, I., 'Don't Clone Humans!' *Science*, Volume 291, 30 March 2001, p.2552

43 Dr Eloise Piercy, *Submissions,* p.S582. See also World Federation of Doctors Who Respect Human Life, *Submissions,* p.S800; David Elder, *Submissions*, p.S199

44 World Federation of Doctors Who Respect Human Life, *Submissions*, S.801; Ms Maryke Vaartjes, *Submissions,* p.S128; Dr Peter McCullagh, *Submissions*, p.S315. AHEC report; Chapter 2, paragraphs 2.46-2.47

45 Dr Peter McCullagh, *Submissions*, p.S313; Professor Robert Norman, *Transcript*, p.73; Ethics Committee, Royal Australasian College of Surgeons, *Submissions*, p.S568

private sector. Federal funding, which supports public sector research, cannot be used for research on embryos.

Embryonic Stem Cell Research

3.39 Research is now being focused on mouse, monkey and human pluripotential stem cells, in order to guide differentiation to specific cell types in culture with the ultimate aim of providing cells and tissue for the repair of damaged and diseased organs. There have been several successes in animal models: embryonic stem cell-derived cardiac muscle cells were incorporated successfully into damaged rat hearts, and neural cells into the brain of a mouse model of multiple sclerosis.[46] Immature nerve cells derived from mouse embryonic stem cells and transplanted into the damaged spinal cords of rats partially restored spinal cord function.[47]

3.40 Embryonic stem cell research also offers insights into developmental events that cannot be studied directly in the intact human embryo. They can be used to identify targets for new drugs, elucidate mechanisms that facilitate the efficient differentiation of embryonic stem cells to specific cell types, and provide an unlimited source of cells for drug discovery and transplantation therapies.

3.41 Professor Peter Rathjen pointed out that:

> …using embryonic stem cells potentially gives us the ability to produce any kind of cell in any number with any genetic modification, and that potentially opens the opportunity to treat diseases which are currently inaccessible to us.[48]

3.42 Associate Professor Martin Pera spoke of the application of embryonic stem cell technology as he sees it in four areas:

> …basic research into human development and disorders thereof, including birth defects and certain types of childhood embryonal tumours; secondly, the discovery of novel protein factors which may be used to drive tissue regeneration and repair if administered therapeutically; thirdly, the development of *in vitro* human cell models for drug discovery and toxicology in the pharmaceutical industry; and, fourthly, the development of tissue for transplantation…[49]

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46 *Science*, Volume 288, 9 June 2000, p.778

47 *Science*, Volume 286, 3 December 1999, p.1826

48 Professor Peter Rathjen, *Transcript*, p.65

49 Associate Professor Martin Pera, *Transcript*, pp.5-6. See also Professor Julian Savulescu, *Submissions*, p.S649

3.43 The AHEC report identified the benefits to be anticipated from the production of human ES cells 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. To these might be added the acquisition of new information about nuclear-cytoplasmic interactions relevant to studies of ageing and cancer.[50]

3.44 Associate Professor Pera predicted that embryonic stem cell technology is

> …going to have a major impact on biotechnology and on the pharmaceutical industry. It is likely through transplantation medicine to have a major role in what is now called regenerative medicine. …there will be likely spin-offs in agriculture and agricultural biotechnology as discoveries in human ES cell biology are applied to other species. [51]

3.45 Much of the evidence and discussion of embryonic stem cells recognised the value and the significant potential benefits of basic and strategic research on pluripotency of cells and the regulatory steps in cell lineage development. Research to find the cell signals and triggers that govern differentiation may provide alternatives to therapies using the cells, but the stem cell research has to be completed in order to find and characterise these factors. As this inquiry concludes, the pace of the research continues to increase.

Adult Stem Cell Research

3.46 There is growing evidence that many adult organs contain stem cells which retain their ability to divide and transform into a range of different cell types as and when the need arises. This process occurs under the influence of biochemical signals that are not yet understood. The hope is that adult stem cells, like embryonic stem cells, may also be exploited to generate cells for transplantation which are not rejected.[52] Ideally they could be harvested from a patient, grown and multiplied into the desired

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50 AHEC report, Chapter 2, paragraph 2.27

51 Associate Professor Martin Pera, *Transcipt*, p.6

52 Dr Peter McCullagh supports as an alternative approach to solving the tissue transplantation problem the use of adult stem cells. He notes that *Science* identified the production of stem cells for particular tissues as being 'the breakthrough of the year'. Dr Peter McCullagh, *Transcript*, p.67

cell types and used to repair diseased or damaged cells or tissues. The avoidance of an embryo stage would be a major added benefit.

3.47 Research in the areas of identification of adult stem cells is advancing rapidly. Professor Rathjen noted however:

> Even where adult stem cells have been defined rigorously and can be identified *in vivo* and *in vitro*, there have generally been considerable difficulties in maintaining these cells in an undifferentiated state *in vitro*, and in achieving long term and efficient proliferation. It is therefore difficult to grow sufficient cells for therapeutic transplantation. …In the absence of proliferation, effective genetic manipulation of adult stem cells cannot be achieved.[53]

3.48 There is a growing understanding that adult stem cells may be more flexible than previously thought. Recent research has shown that adult stem cells can differentiate into developmentally unrelated cell types such as nerve cells into blood cells.[54] According to Drs Fleming and Pike of the Southern Cross Bioethics Institute:

> Lineage defined progenitor cells [stem cells] in adult tissues may be more plastic than hitherto thought. They might have the capacity to de-differentiate, or be reprogrammed, becoming totipotent stem cells.[55]

3.49 Preliminary research indicates that bone marrow stem cells appear to be very versatile forming brain and muscle cells and liver cell precursors.[56] Brain stem cells in mice have been shown to be surprisingly flexible, becoming nearly every tissue in the body.[57] Adult neural (brain) stem cells previously thought to be committed to becoming various types of nerve cells can de-differentiate and become blood cell precursors.[58] Liver cells have been derived from human blood stem cells.[59]

3.50 According to a House of Commons Research paper, umbilical cord blood which has the advantage of being readily available, is rich in stem cells but these appear to have limited ability to differentiate, that is, they may only

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53 Professor Peter Rathjen, *Submissions*, p.S766. See also Associate Professor Martin Pera, *Transcript*, p.6

54 'Adult stem cells may be redefinable', *British Medical Journal*, Volume 318, 30 January 1999, p.282

55 Drs Fleming and Pike, *Submissions*, p.S563

56 *Science*, Volume 287, 25 February 2000, pp.1419-1419

57 'Generalized Potential of Adult Neural Stem Cells', D.L.Clarke et al., *Science*, Volume 288, 2 June 2000, pp.1660-1663

58 *Science* , Volume 283, 22 June 1999, pp.534-537

59 *Nature*, Volume 406, 20 July 2000, p.257

produce blood cells or bone marrow cells. Some foetal tissues are also rich in stem cells.[60]

3.51 The paper went on to say that stem cells from cord blood and foetal tissue

> … are already partially committed in development, and it is as yet uncertain what potential exists for differentiation of foetal and umbilical cord blood stem cells into different tissue cells other than those from which they were derived. In the future it may be possible to change the programming of these stem cells so that they mature into other types of tissue.
>
> Stem cells from primitive sex cells of foetuses up to about 6 weeks of development (that are destined to develop into eggs and sperm) have a greater potential to differentiate. They have a similar capacity to develop into other kinds of tissues as embryonic stem cells—they could be termed pluripotent.[61]

3.52 The Royal Society urged that 'the potential of umbilical cord stem cells should be explored vigorously as a high priority' but pointed out the disadvantages of adult stem cells:

> …they are small in number and often hard to access. By the time they have been multiplied up in culture to a therapeutically useful stock of cells their proliferative lifespan may have become dangerously short.[62]

3.53 The AHEC report considered:

> 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.[63]

3.54 While embryonic stem cells tend to differentiate spontaneously into all kinds of tissue, adult stem cells do not spontaneously differentiate but can be induced to do so by applying appropriate growth factors or other external cues. However, one drawback of adult stem cells is that some seem to lose their ability to divide and differentiate after a time in culture. This short life span might make them unsuitable for some medical applications.[64]

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60 House of Commons Research Paper 00/93, (United Kingdom) 13 December 2000, p.22

61 House of Commons Research Paper 00/93, (United Kingdom.) 13 December 2000, pp.22-23

62 *Stem Cell Research- second update*, Policy document 9/01, June 2001, p.2, www.royalsoc.ac.uk

63 AHEC report, Chapter 2, paragraph 2.38. See also Dr David Gawler, *Submissions*, p.S625

64 *Science*, Volume 287, 25 February, 2000, p.1419

3.55 There were concerns expressed in evidence to the Committee that stem cells, including embryonic stem cells, which have an inherent capacity for proliferation are aberrant. The World Federation of Doctors Who Respect Human Life considered:

> Before the full potential of neural stem cells can be realized, we need to learn what controls their proliferation, as well as the various pathways of differentiation available to their daughter cells.
>
> The definition of a cell with a capacity for prolonged proliferation with retention of its undifferentiated form, could be that of a cancer cell.[65]

3.56 Examples of adult stem cell research include the isolation and growth of human mesenchymal stem cells that have been made to develop into fat, tendons, muscle and bone marrow cells,[66] and stem cells isolated from fat removed by liposuction have been grown into muscle, cartilage and bone cells.[67] Neural stem cells have recently been extracted from the brains of mice and, under specific conditions in the laboratory, been made to differentiate into muscle cells. According to the scientists involved this is the first 'unequivocal' evidence that adult stem cells, like embryonic stem cells, could develop into different tissue types.[68]

3.57 The Spinal Cord Society, a consumer based organisation with members in over 37 countries around the world, has developed a technique for growing human adult neuronal stem cells for treatment of Parkinson's disease. It has received approval from the US Food and Drug Administration (FDA) to proceed to a Phase II clinical trial. The Society is also attempting to derive neuronal (nerve) cells from bone marrow cells and hopes to derive stem cells from even more convenient sites, such as skin, and is also stimulating stem cells *in situ* by altering the local micro-environment of cells, leading to differentiation and repair *in situ*.[69]

3.58 Biochemical cues for transformation and control of adult stem cells are poorly understood. Better understanding of how to control adult stem cells is crucial for their prospects in regenerative medicine or tissue

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65 World Federation of Doctors Who Respect Human Life, *Submissions*, S.800. See also David Elder, *Submissions*, p.S199

66 Dr Mark Pettinger and colleagues at Osiris Pharmaceuticals and the Johns Hopkins School of Medicine. *Science*, Volume 284, No. 5411, 2 April 1999, pp.143-146

67 Patricia A. Zuk *et al*, 'Multilineage cells from Human Adipose Tissue: Implications for Cell-Based Therapies'. *Tissue Engineering*, Volume 7, No.2, pp.211-228

68 *Nature*, Volume 412, pp736-739 (2001); *Sydney Morning Herald*, 16 August 2001, p.1, referring to Dr Perry Bartlett of the Walter and Eliza Hall Institute of Medical Research, Melbourne. Earlier work demonstrated that mouse neural stem cells could change into blood cells

69 Spinal Cord Society, *Submissions*, pp.S853-54, *Exhibit* 32

replacements and this understanding may depend on embryonic stem cell research. The AHEC report comments that the 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 suggested that:

> It is likely "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.[70]

3.59 This appears to be supported by recent research. An Italian group led by Drs Vescovi and Cossu reported in *Nature Neuroscience:*

> …that nerve stem cells from an adult were more flexible than thought and could give rise to skeletal muscle. When placed in contact with other neural stem cells, they give rise to neurons and glia. … But neural stem cells in contact with muscle gave rise to muscle.[71]

3.60 Dr Vescovi, co-director of the Institute for Stem Cell Research in Milan, stated:

> "…we are far from showing that adult stem cells equal embryonic stem cells with respect to their growth potential and plasticity". … It was not possible to say whether any adult stem cell could turn into any tissue, depending on where it was in the body. … I hope, though, that this is the case. "The implications for therapy of human diseases would be astounding…"[72]

3.61 Adult stem cells may offer advantages over embryonic stem cells in that ideally they could be harvested relatively simply (compared to somatic nuclear transfer to form an embryo) from patients, transformed in the laboratory and transferred back to patients. Such auto-transplants would avoid both graft rejection problems and risks of graft to host viral infection.

3.62 Although there are many advocates for the adult stem cell approach and recent reports in the media suggest that this research is advancing rapidly, many scientists agree that embryonic stem cell research is, for the time being, crucial to further understanding and progress. They dispute the assertion that adult stem cells will replace embryonic stem cells in their importance for either basic or applied studies in the near future. The American Academy for the Advancement of Science wrote to President Bush:

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70 AHEC report, Chapter 2, paragraph 2.41

71 House of Commons Research Paper 00/93, p.24. (United Kingdom)

72 House of Commons Research Paper 00/93, p.24. (United Kingdom)

> One of the misconceptions held by some is that study of adult stem cells will be sufficient to realize the medical promise of this line of research. But the prevailing view of expert scientific opinion is that it is far too early to know if adult stem cells have the same potential as embryonic stem cells. It is important to convey to the public the limitations of the research on adult stem cells. It is likely to take years to discover whether adult stem cells will be effective in treating many diseases that may be treatable sooner with embryonic or fetal stem cells.[73]

3.63 A similar view is expressed by Irving L.Weissman and Nobel Laureate David Baltimore:

> Although HSCs (Haematopoietic Stem Cells) capable of regenerating the blood can be isolated from adults or fetuses, so far brain stem cells capable of robust growth and transplantability have come only from fetal or ESC (Embryonic Stem Cell) sources. This is likely to be true for a number of tissues; fetal stem cells are much more active than postneonatal cells. A moratorium on research and / or transplantation of fetal stem cells could thus be devastating. As for the search for pluripotent adult stem cells, it is always possible, perhaps even likely, that further research might reveal a source. But that is simply a hope, and it would be foolish to abandon the surer path for the unproven one.[74]

3.64 The Royal Society also believes that:

> …adult stem cell research and embryonic stem cell research **are not alternatives** and **both** (emphasis in original) must be pursued. In all likelihood each will yield distinctive therapeutic benefits but (i) we cannot predict which will be first or better and (ii) work on one system may help work on the other.[75]

Transdifferentiation Or Dedifferentiation

3.65 Somatic cell nuclear transfer and the derivation of embryonic stem cells provide one method for obtaining tissue for repair and transplantation. Adult stem cell technologies may provide another. Alternative technologies suggested by the Australian Academy of Science included full or partial reversal of differentiation of adult cells.[76]

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73 http: / / www.aaas.org / spp / dspp / sfrl / projects / stem / bushltr.htm, 6 March 2001.

74 Weissman, I. L., and Baltimore, D., *Science* ,Volume 292, 27 April 2001, p.601

75 *Stem Cell Research- second update*, Policy document 9 / 01, June 2001, www.royalsoc.ac.uk

76 Australian Academy of Science *On Human Cloning. A position statement*, 4 February 1999, p.15

3.66 Transdifferentiation or dedifferentiation, (full or partial reversal of differentiation) is the process of taking an adult cell of one tissue type and, through a cellular process yet to be understood, reprogramming it to form a different type of tissue for transplantation. Associate Professor Pera said of this possibility:

> There are some very exciting recent advances in that area and it has some potential, but I have to point out to you that the mechanism, and even a basic phenomenology of what is going on in these experiments, is very poorly understood at present and it may be a long time before we know how to control that process.[77]

3.67 Professor Rathjen stated:

> There is therefore some reason to believe that pluripotent cells might ultimately be attained by direct dedifferentiation of somatic cells. This would provide a route to generation of ES cells in the absence of embryonic intervention. [78]

3.68 Professor Rathjen referred in his submission to worldwide interest in cell 'deprogramming':

> Publications already show "dedifferentiation" of adult CNS stem cells into neural lineages in rat neonates, differentiation of bone marrow to hepatic lineages and skeletal muscle following transplantation, and differentiation of cells derived from skeletal muscle to haemopoietic cells *in vivo*. The initial results therefore support the contention that microenvironments within the mammal retain signals that can direct the fate of transplanted cells to a locally appropriate outcome.[79]

3.69 The submissions and evidence show the growing worldwide research effort that is being directed towards the understanding of differentiation and transdifferentiation of many cell types. It may be some time, however, before scientists know how to control the process.

RESEARCH INVOLVING HUMAN EMBRYOS

3.70 Although a great deal of effort is being invested in new technologies to avoid the use of embryos, it is not possible yet to study early differentiation, cell lineage choice and multipotency without embryo-derived stem cells. Consequently, the derivation of embryonic stem cell

77 Associate Professor Martin Pera, *Transcript*, p.6

78 Professor Peter Rathjen, *Submissions*, p.S767

79 Professor Peter Rathjen, *Submissions*, p.S767

lines will involve the use of embryos until adequate alternatives are developed.

3.71 Professor Trounson noted:

> There is no way in which anybody can derive the base cell lines that are of interest through any other way than making embryonic stem cells.[80]

However, the needs may be limited:

> If we want to derive four new lines of embryonic stem cells we would theoretically use eight embryos and we would not really want to use any more ever again. We would have enough cells there to supply all the research institutes in Australia, and probably world-wide…[81]

3.72 Mr Robert Klupacs submitted that the use of embryos beyond the derivation of initial cell lines would be limited. The patient could be treated with new anti-rejection drugs or immunised with their own antigens to overcome the immunological incompatibility between donor and recipient.[82]

> Our aim is to produce stem cells which can be used as "Universal Donors". That is, they can be derived from couples who have donated excess embryos after the completion of IVF treatment for the purpose of creating stem cells which can then multiply into large numbers and be used for transplantation into anyone requiring treatment…
>
> The "Universal Donor" approach means that the cell lines which we currently have which have been derived from only 12 embryos, will most likely be sufficient to provide cell therapies for Australia and other countries. It is unlikely that any further embryos will ever be required.[83]

3.73 The Committee queried claims that a limited number of stem cell lines can supply all demands and therefore no new research on embryos will be required. These claims ignore the related issues of a potential monopoly position[84] of cell lines and the associated intellectual property. Before

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80 Professor Alan Trounson, *Transcript*, p.5

81 Professor Alan Trounson, *Transcript*, p.4

82 Mr Robert Klupacs, *Transcript*, p.187

83 Mr Robert Klupacs, *Submissions*, pp.S892-893

84 http://theage.com.au/news/state/2001/08/28/FFXIZRRBVQC.html There is already resentment amongst US scientists over the control that Geron Corporation, the biotechnology company that claims it has "worldwide exclusive commercial rights" to stem cells, seeks over their work

clinical applications could be developed for specific individuals and specific diseases, it is likely that more embryos will be necessary unless new research obviates the need for embryos as a source of cells.

3.74 Stem cells derived from embryos are essential for research aimed at understanding early human developmental processes and disorders thereof and potential new contraceptive approaches. According to Associate Professor Pera:

> These early embryonic cells may be the only way to identify new factors that are active on early, very primitive, progenitor cell populations… Finally and most importantly, basic research on embryonic stem cells will teach us what pluropotentiality is. What is a primitive undifferentiated cell? What gives it the ability to turn into all those types of adult tissues? It is really this basic research, perhaps the identification of key genes that control that feature of embryonic stem cells, that may eventually teach us how to eliminate the need for embryos and how to reprogram adult cells.[85]

3.75 Currently, somatic nuclear transfer resulting in an embryo stage is the only way to derive deprogrammed cells. New techniques are being researched and developed, for example, *New Scientist* reports that a type of mouse white blood cell was deprogrammed following fusion with a mouse embryonic germ cell.[86] Professor Rathjen alluded to research in this direction:

> …many scientists are hopeful that it will prove possible to revert a somatic nucleus to a more primitive, pluripotent state by intercellular nuclear transfer. This would occur in the absence of oocyte injection and creation of a viable embryo.[87]

3.76 In summary, alternative sources for the derivation of pluripotent or multipotent cells may become available. It is unclear when this will happen, or if such availability will remove or reduce the need for embryos in stem cell research.

85 Associate Professor Martin Pera, *Transcript*, p.6

86 *New Scientist*, 29 January 2000, p.4

87 Professor Peter Rathjen, *Submissions*, pp.S767-768

SUMMARY

3.77 The Committee considered the AHEC report and recognised the thoroughness of its review. It noted that a great deal of progress and new discovery has been made in the science since the report was published.

3.78 The Committee noted the recent scientific breakthroughs that have shaped this field, the very rapid pace of current scientific development and the prospect for further new discovery and applications. In particular, the Committee agreed that current knowledge and definitions may change further as a greater understanding of the fundamental principles in cell and developmental biology is achieved.

3.79 Although the scientific basis of this new field is becoming established, many other facets of cell regulation and transdifferentiation may be found. New approaches may remove the need to use embryos and embryonic stem cells, while identification of cell signals and triggers of differentiation may form the basis of new therapies. Consequently, the monitoring and further review of the field, by a delegated authority at appropriate intervals, will be necessary.