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CLONING ISSUES IN REPRODUCTION, SCIENCE AND MEDICINE.

A Consultation Document

Human Genetics Advisory Commission
and
Human Fertilisation & Embryology Authority

January 1998

Cloning Issues in Reproduction, Science and Medicine

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Section 1

INTRODUCTION

1.1 In 1997, Dolly the sheep, the first vertebrate cloned from a cell of an adult animal, generated considerable interest. Although hailed as a remarkable scientific breakthrough, concern was raised both nationally and internationally about the future evolution of this technology, particularly in the context of the cloning of human beings.

1.2 The Human Genetics Advisory Commission (HGAC), which reports to Ministers on issues arising from new developments in human genetics that can be expected to have wider social, ethical and/or economic implications, and the Human Fertilisation and Embryology Authority (HFEA), which has regulatory responsibility for the Human Fertilisation and Embryology Act 1990, decided to hold a consultation exercise on cloning. A working group, consisting of members of both bodies, was established to take this forward.

1.3 This consultation paper has identified different potential uses of cloning technologies, as this will help to identify the various ethical issues involved. For the purposes of this consultation we draw the distinction between two types of cloning: on the one hand, human reproductive cloning, where the intention is to produce identical fetuses or babies; and, on the other hand, what may broadly be called therapeutic cloning, which (although not coterminous with conventional scientific usage) includes other scientific and medical applications of nuclear replacement technology. For example, studying cell development or creating stem cell lines with the aim of developing therapeutic applications. In order to make this consultation as comprehensive as possible, some of the ethical questions raised relate to practices which are illegal in the United Kingdom. Some embryo research proposals would require

regulations to be made by the Secretary of State for Health before they could be carried out. Further details of the UK's legal framework are given at Section 5. This paper also discusses whether current science raises new questions about more abstract concepts such as individuality and human dignity. It seeks the views of the community, including specialists drawn from organisations with scientific, legal, clinical or ethical interests. It is envisaged that this paper will be revised in the light of comments received, and form the basis of advice from the HGAC and HFEA to Ministers.

Section 2

DOLLY AND POLLY

2.1 Dolly is the first example of an adult vertebrate cloned from another adult by any technique. She was cloned using a nuclear replacement technique, where the nucleus from a cell, which had two chromosome sets, was fused with an unfertilised egg from which the nucleus had been removed. This experiment was the first time that a fully developed animal had been born following transfer of a somatic cell nucleus from an adult animal. A major motivation for the work was to improve methods for the genetic improvement of livestock. The technology could also be used to improve the efficiency of production of transgenic livestock. This could have potential benefits, for example, in increasing production of human proteins in the milk of transgenic animals (e.g. proteins used to treat blood clotting disorders such as haemophilia).

2.2 Dolly was the result of a collaborative experiment between the Roslin Institute and PPL Therapeutics PLC to test the suitability of different sources of

cells for nuclear replacement. She was derived from cells taken from the udder of a 6 year old Finn Dorset ewe which were then cultured in the laboratory. 277 of these cells were then fused with 277 unfertilised eggs, from which the nucleus had been removed, to create "reconstructed eggs". This process resulted in 29 viable reconstructed eggs, each with a nucleus from the adult animal, which were then implanted in surrogate Blackface ewes. One gave birth to Dolly[1].

2.3 However, Dolly was not the first sheep to be created using nuclear replacement technology. In 1996[2], it was reported that sheep embryos had been cloned using nuclear replacement and had resulted in the birth of two genetically identical sheep, Megan and Morag. The difference between Dolly and Megan and Morag is the nuclear donor source: Dolly is derived from an adult sheep, Megan and Morag from a sheep embryo.

2.4 Recently, the Roslin Institute and PPL Therapeutics PLC announced the birth of Polly. She is a transgenic sheep produced by transfer of the nucleus of a cultured fetal fibroblast. She carries a human gene for blood clotting Factor IX, which is used for treatment of haemophilia[3].

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[1] "Viable Offspring Derived from Foetal and Adult Mammalian Cells", Nature, 27 February 1997, p.811.

[2] "Sheep Cloned by Nuclear Transfer from a Cultured Cell Line", Nature, 7 March 1996, pp 64-6.

[3] "Transgenic Sheep Expressing Human Factor IX", Science, 19 December 1997, p.2130-2133

Section 3

WHAT IS CLONING?

3.1 The birth of Dolly aroused interest and controversy all over the world, especially focusing on the possibility of human reproductive cloning, namely the production of genetically identical human beings.

3.2 The term "cloning" applies to any technique used to produce clones. The etymology of the term "cloning" is the Greek for "twig". Considerable confusion was caused because the term "cloning" has been used in both loose and conventional ways for many years to describe a number of entirely different concepts. It is important that stringent definitions be adopted and that the precise context be defined on a consistent basis to avoid such confusion. As mentioned in the introduction, for the purposes of clarity in this document we will use two distinct meanings of "cloning".

3.3 Firstly, "reproductive cloning", that is, where an entire animal is produced from a single cell by asexual reproduction. The creation of Dolly falls into this category, although this paper does not consider the implications of animal cloning. Our concern is with "human reproductive cloning", which would involve the creation of a human being who was genetically identical to another.

3.4 Secondly, there are scientific and therapeutic applications of nuclear replacement technology, which do not involve the creation of genetically identical individuals. These activities are also sometimes referred to as "cloning", and may broadly, (although not coterminous with conventional scientific usage) be referred to as **"therapeutic cloning"**. These applications may include therapy for human mitochondrial disease and research which might

lead to the replacement of damaged or diseased tissues or organs, without the risk of rejection reactions. For example, skin tissue to treat patients suffering from burn injuries (see Section 7).

3.5 In addition, there are some routine techniques long practised by the scientific and medical communities, which are not the subject of this consultation:

a) generating multiple identical copies of genes or gene fragments (the chemical nucleotide sequences of nucleic acids DNA and RNA). These techniques have been used for over 20 years.

b) cultivation in the laboratory of single cell organisms such as bacteria and fungi, or individual animal or human cells to produce multiple identical single cells. For example, industrial fermentation processes for the production of bread, beer, wine. These techniques have been used extensively in biomedical research for over 50 years.

c) The production of entire plants from a single cell or several cells by asexual reproduction e.g. the taking of cuttings which has been practised in horticulture for centuries.

3.6 Sexual reproduction (whether plants, micro-organisms, animals or humans) involves the mixing or recombination of genetic material derived from two donors. For example, the fertilisation of an egg by a sperm to produce a progeny with a unique identity. Genetically identical individuals can still arise, however, from sexual reproduction under circumstances in which an early stage embryo created by natural fertilisation (or in vitro fertilisation) undergoes division to form two or more identical births. This is a natural form of cloning, which resembles the experimental production of animal clones by embryo splitting described in 4.1 below.

Section 4

ARTIFICIAL CLONING TECHNIQUES

4.1 The prefix "artificial" has been adopted in the title of this section to emphasise the role of scientific and/or clinical intervention in producing the cloned progeny. Two distinct methods have been used to clone animals and could thus, in theory, be used to clone human beings:

Embryo splitting

The artificial division of a single embryo replicates the natural process which can give rise to identical twins. In this case, both the nuclear genes and the small number of mitochondrial genes would be identical. This is done by separating embryonic cells at a very early stage of development before they have had a chance to differentiate. However, there are very few cells at this stage - usually less than eight - so this method can only give rise to a few clones.

Nuclear replacement

This process involves the introduction of genetic material (in the form of an individual cell nucleus removed from either an embryonic, a fetal, or an adult cell) into the cytoplasm of an unfertilised egg or embryo, whose own genetic material (nucleus) has been removed. The nuclear genes of clones produced by this technique would be identical, although the mitochondrial DNA of such clones would be different. However, unlike the embryo splitting technique, nuclear replacement has the potential to create a clone of an adult organism, as well as the potential to produce many more clones.

4.2 The nuclear replacement technique to clone animals is relatively new. The first evidence that it was possible to clone vertebrate animals using nuclear replacement was in 1952[4], using frogs. The more recent developments of nuclear replacement technology have brought with them the potential to contribute towards the genetic improvement of livestock. Annex C discusses in more detail the experiments which led to Dolly and subsequent developments.

4.3 The uses of animal reproductive cloning, including the multiplication of those with desirable characteristics and the creation of animals with new characteristics by genetic targeting, are not considered in this paper. The Ministry of Agriculture, Fisheries and Food's (MAFF) policy on the cloning of farm animals has been guided by the Report of the Committee to Consider the Ethical Implications of Emerging Technologies in the Breeding of Farm Animals (the Banner Committee) which reported in 1995. MAFF has since asked the Farm Animal Welfare Council to consider the implications of cloning for the welfare of farmed livestock. A consultation exercise was recently held.

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[4] Briggs and King: "Transplantation of living nuclei from blastula cells into enucleated frog's eggs", Proceedings of the National Academy of Sciences (USA)38: 455-463, 1952.

Section 5

LEGAL FRAMEWORK

5.1 The creation, use and storage of human embryos outside the body is regulated under the Human Fertilisation and Embryology Act 1990 (HFE Act) by the Human Fertilisation and Embryology Authority (HFEA). The regulatory framework encompasses, among other things, in vitro fertilisation (IVF), donor insemination, and research involving the creation or use of human embryos. Anyone undertaking, without an HFEA licence, an activity governed by the HFE Act may be guilty of a criminal offence.

5.2 The nuclear substitution of an embryo, or any cell whilst it forms part of an embryo is expressly prohibited by the HFE Act. Embryo splitting and nuclear replacement of eggs are not expressly prohibited, but as both involve the use or creation of embryos outside the body, they fall within the HFE Act and therefore come under the jurisdiction of the HFEA.

5.3 The HFE Act allows, under a licence from the HFEA, research involving human embryos within strict limits which must not exceed the fourteenth day of their development. Embryos used for research must not be replaced in a uterus. The HFEA can license the use of human embryos only where it considers their use to be necessary for the research; therefore animal studies must often have been carried out before research involving human embryos will be permitted. In addition, any such research must appear to the HFEA to be necessary or desirable for one of the following purposes[5]:

- to promote advances in the treatment of infertility;

[5] HFE Act 1990 Schedule 2 paragraph 3 (2). HMSO

- to increase knowledge about the causes of congenital disease or about the causes of miscarriages; or

- to develop more effective techniques of contraception or methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation.

This list may be extended by the Secretary of State for Health in regulations, provided the new categories are established with a view to increasing knowledge about the creation and development of embryos, or about disease, or with a view to enabling such knowledge to be applied[6].

5.4 The HFEA's policy is that it will not license any research which has reproductive cloning as its aim. However, it would consider licence applications for other types of research involving embryo splitting or nuclear replacement in eggs, provided that the research falls within one of the purposes specified by the HFE Act, or any regulations, which may be made by the Secretary of State for Health as described above.

5.5 The Warnock Committee (1984)[7], whose report eventually led to the HFE Act, made clear its view that human reproductive cloning should not be permitted. In its deliberations on, "The Cloning of Animals from Adult Cells"[8], the House of Commons' Science and Technology Committee, was concerned that the law needed to be reviewed to take account of scientific developments since then.

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[6] HFE Act 1990 Schedule 2 paragraph 3 (3)

[7] Report of the Committee of Inquiry into Human Fertilisation and Embryology, HMSO, July 1984.

[8] "The Cloning of Animals from Adult Cells", House of Commons Science and Technology Committee, Session 1996-97, Fifth Report (printed 18 March 1997), Vol. I

5.6 In its response to the Committee[9], the Government has indicated that, while human reproductive cloning cannot take place in the UK, it will consider carefully, in the light of developments, whether the legislation needs to be strengthened in any more specific way. It has said that, in respect of cloning, it will take into account the views of Members of Parliament, the HGAC, HFEA and responses to any general consultation on the broader issues.

Section 6

REACTIONS TO THE ANNOUNCEMENT OF THE CLONING OF DOLLY

6.1 There was extensive and mixed press coverage of Dolly. Most of the reporting focused on the prospect of human reproductive cloning and the issues raised by such a possibility.

6.2 The UK Government confirmed its position that work which would create cloned human beings should not and cannot lawfully be carried out. Tessa Jowell, Minister for Public Health, made the position clear: *"We regard the deliberate cloning of human individuals as ethically unacceptable"*[10].

6.3 President Clinton called on the US National Bioethics Advisory Commission (NBAC) to investigate the ethics of such procedures. He also gave

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[9] "The Cloning of Animals from Adult Cells", Government Response to the Fifth Report of the House of Commons Select Committee on Science and Technology, Session 1996-97, (Cm 3815), Page 4, paragraph 17

[10] House of Commons Official Report, Parliamentary Debates (Hansard) 26 June 1997, Column 615.

instructions to the heads of executive departments and agencies that *"no federal funds shall be allocated for cloning of human beings"*. The NBAC, publishing its report on 9 June 1997, concluded that using nuclear replacement technology for the purposes of creating a child was unsafe, and recommended legislation to ban research into the cloning of *"complete people"*. The proposed legislation should have a five year "sunset" clause to allow review on the continued desirability of prohibition. President Clinton accepted this and has sent the "Cloning Prohibition Bill 1997" to Congress for consideration. In doing so he stressed the potential benefits of nuclear replacement technologies and pointed out that the Bill did not seek to stop these from being realised. The Bill, as of January 1998, is still being considered by Congress.

6.4 Dolly caused a global sensation and since her announcement a number of international instruments have been developed. The UK has been closely involved in a number of initiatives which call for the reproductive cloning of human beings to be banned:

- EC draft Biotechnology Patents Directive[11] which forbids the issue of a patent on work leading to deliberate cloning of human beings.

- A protocol forbidding the cloning of human beings has been developed under the Council of Europe Bioethics Convention[12].

- A UNESCO Declaration on the Human Genome and Human Rights, adopted on 11 November 1997[13], of which Article 11 states that

[11] European Parliament and Council Directive on the legal protection of biotechnological inventions COM(97) 446 final

[12] 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. Strasbourg: Council of Europe 1996 (ETS 164)

[13] "Universal Declaration on the Human Genome and Human Rights", published by UNESCO, November 1997

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

6.5 Annex D contains brief details of laws in some countries in respect of human cloning.

Section 7

POTENTIAL RESEARCH AND THERAPEUTIC BENEFITS: ETHICAL IMPLICATIONS

7.1 The creation of Dolly represented a further step in the development of nuclear replacement technology. It showed that a nucleus taken from an adult animal could be reprogrammed to allow the full range of gene expression needed to produce a complete animal, so called gene totipotency. Although this research is still in its early stages and has not been reproduced it is a significant scientific breakthrough and offers a number of basic research applications of human relevance.

7.2 Nuclear replacement research can improve our knowledge about physiological processes and the genotype. For example, it is hoped that this work will offer a greater insight into the origins of cancer and other cellular development processes such as ageing and cell commitment. It may also offer the potential to produce better animal models for human disease which would aid research into new or improved therapies. Many of these important questions will be difficult to study unless the procedure shown in livestock animals can be extended to mice, for example.

7.3 In humans, the possibility of using nuclear replacement technology for reproductive cloning has been raised. However, it could also be used as a means to avoid the transmission of inherited diseases derived from the mitochondria. This possible application need not involve human reproductive cloning. It could involve, for example, taking an enucleated egg from a donor containing normal mitochondria, which would then receive the nucleus from an unfertilised egg taken from the individual with mitochondrial disease. The reconstructed egg could then be fertilised. This type of therapy would not involve the production of a genetically identical individual or fetus.

7.4 It is important to make the distinction between human embryo research, which may be permitted under licence under the 1990 Act and reproductive cloning, where an embryo is implanted into a woman's womb. The Warnock Committee concluded in 1984 that, *"the embryo of the human species ought to have a special status"*, which should be enshrined in legislation. The Committee stated that this special status should not afford the human embryo the same status as a living child or an adult, but did mean that human embryos should not be used frivolously or unnecessarily. The Committee went on to conclude that the special status of the embryo would permit some embryo research up to the fourteenth day of development provided the research was strictly controlled and monitored. The recommendations of the Warnock Committee were included in the provisions of the Human Fertilisation and Embryology Act 1990, which allows research to be carried out on embryos up to 14 days development under licence from the HFEA within certain restrictions. **Would the use of nuclear replacement techniques or embryo splitting to create embryos raise any new issues in relation to the special status of the human embryo?**

7.5 Embryo research which involved nuclear replacement technology or embryo splitting in the UK would not be allowed to lead to any fetuses or babies being produced. A non-reproductive application of this technology

would be to use the nuclear replacement technique to create in-vitro stem cells. **Are there any medical or scientific areas that might benefit from research involving the creation of a cloned human embryo ? Would embryo research involving nuclear replacement technology raise any new issues in respect of what may ethically be done within the 14 day period?**

7.6 Research which might generate in-vitro stem cells and cause them to differentiate into specific cell types could provide insights into how to induce regeneration of damaged human tissue without risk of rejection reactions. For example: neural tissue for sufferers of Parkinson's Disease; skin tissue to treat patients suffering from burn injuries; and muscle tissue to treat patients suffering from heart damage. Under the HFE Act 1990, limited human embryo research may be licensed for specific purposes as defined in the Act. However, the Secretary of State does have the power to broaden the scope of this research, which would permit the HFEA to consider proposals to conduct human embryo research for some therapeutic purposes (see paragraph 5.3). **Would any of the potential applications of nuclear replacement, some of which are exemplified above, that would not result in cloned fetuses or babies raise any new ethical concerns?**

Section 8

HUMAN REPRODUCTIVE CLONING: THE ETHICAL IMPLICATIONS

8.1 The use of either embryo splitting or nuclear replacement deliberately for the purposes of human reproductive cloning, to produce genetically identical human beings, raises serious ethical issues, concerned with human responsibility and instrumentalisation of human beings.

8.2 Cloning by embryo splitting would artificially reproduce the natural process by which monozygotic (identical) twins, who make up approximately one third of twins in the UK, are produced. World-wide, there are approximately 3-4 monozygotic twinnings per 1000 births. Such naturally occurring twins show that genetically identical individuals are far from being identical people: they may differ from one another physically, psychologically, in personality and in life experience. The intrauterine environment may cause lasting differences. It is reported that some monozygotic twins have problems in establishing their identity and experience delayed language development and problems forming other relationships. It is also reported that these difficulties usually arise when the children have been treated as an indistinguishable and inseparable pair. If individual humans were cloned by nuclear replacement from an adult cell, they would, of course, be even more different from their donor, since their mitochondria, their age, their environment, both before and after birth, and their upbringing would differ. The experience of natural identical twins suggests that a unique genetic identity is not essential for a human being to feel, and be, individual[14]. **Therefore what is meant by the assertion that individuals have the right to their own genetic identity ? What does this mean for identical twins ?**

8.3 There are a number of situations where it has been suggested that cloning technology could be applied to make a "copy" of another human being. As explained in Section 5 none of the activities suggested in these scenarios are permitted in the UK. Such scenarios envisage single or multiple "copies" of a living or dead fetus, baby, child or adult. For example:

- Parents might wish to "replace" an aborted fetus, dead baby or child killed in an accident. A grieving woman whose husband and daughter have been killed in the same car crash, may wish to use the DNA from

[14] Wright L. Twins, genes, environment and the mystery of human identity. London: Weidenfeld and Nicholson. 1997.

one of her daughter's cells and insert it into an egg supplied by another woman. The child born would be a clone of her dead daughter. However, the mother would not be "getting back" the same child that had died.

- In the case of a child dying of kidney failure and where neither parent can donate a compatible organ, parents might wish to have a further sibling, produced by cloning, to be a compatible organ donor, as this would avoid a rejection reaction. One of this child's kidneys might then be transplanted to save the life of their older sibling.

- An individual might seek to use cloning technology in an attempt, as that individual might see it, to cheat death.

There are moral arguments to support the claim that human dignity forbids the use of human beings only as a "means", holding that they are to be treated as an "end" in their own right. **What implications do these considerations have for the ethics of human reproductive cloning?**

8.4 There are many general questions about intervention and reproductive technology, which are not unique to cloning. For example, what limits are there on the role of prior choice of characteristics in offspring, where this is scientifically made possible. These presumably apply equally to cloning and include the obvious need for safety issues to be addressed fully.

8.5 A potential application of human reproductive cloning by nuclear replacement might be to assist human reproduction. A lesbian couple might wish to have a child. Here the cell nucleus from one woman could be inserted into an enucleated egg from the other. The resulting embryo might then be implanted in the uterus of the woman who donated the egg. Another scenario

might be where both individuals of a couple are infertile or where the prospective father has non-functional sperm. In this case, cloning one member of the couple to create offspring might be envisaged. **Would the use of nuclear replacement techniques be beyond the limit of what is ethically acceptable to resolve a couple's infertility problem ?**

8.6 Irrespective of whether it would be desirable, there is considerable doubt about whether it would even be possible to clone humans using the techniques used to produce Dolly the sheep. The nuclear replacement technology used to produce Dolly is still in its early stages. We do not yet know whether the work which created Dolly is repeatable in animals, nor is it known whether it can be replicated in humans. We should bear in mind that Dolly was the only normal lamb born from 276 similar attempts. Only 29 resulted in implantable embryos, all of which, except the one leading to Dolly, resulted in defective pregnancies or grossly malformed births. Similar procedures aimed at human cloned reproduction might be associated with similar "wastage" rates and uncertainties about malformations. The age of Dolly's DNA may be the same as the original sheep, of which she is a clone. She may have a shortened life-span or a greater susceptibility to cancer. Even though she appears to be fertile, her progeny may show an increased abnormality rate, owing to the accumulation of damage to the DNA. This raises safety issues about the development of nuclear replacement for therapeutic purposes. Any attempt to develop this technology in humans would be expensive and would require a large amount of human experimentation. **Do these considerations make experimentation in humans involving the implantation of cloned embryos ethically unacceptable? How does this case differ from the experiments that first led to successful in vitro fertilisation (IVF) procedures?**

8.7 IVF and embryo splitting are technological interventions that mimic natural physiological processes (i.e. fertilisation and the natural creation of monozygotic twins or triplets). In contrast, there is no apparent known natural

counterpart for the transfer of genomes by nuclear replacement. IVF is currently used to promote the creation of human beings that could not be brought into being under natural conditions. **Is there a distinction between different artificial technologies according to whether they have natural counterparts or not? Should society adopt a graded scale of "unnaturalness" with some variation from the natural regarded as being unacceptable?**

Section 9

YOUR COMMENTS

9.1 The HGAC and HFEA would very much welcome your general comments on how the technology might actually develop, the opportunities and problems that would be raised by human reproductive cloning and other applications of nuclear replacement technology. We are also interested in your views on the priorities for the future and the ethical setting in which these scientific developments are taking place, including any additional ethical issues raised by human cloning that you have identified. It would be helpful if your response could be structured around the questions set out below:

Any new issues in 14 day period (paragraphs 7.3 - 7.6)

Q1 Would research using nuclear replacement technology raise any new ethical issues in relation to what is permitted in work with embryos in the 14 day period?

Q 2 Are there any medical or scientific areas that might benefit from research involving human nuclear replacement?

Own genetic identity (paragraph 8.2)

Q3 To what extent can a person be said to have a right to an individual genetic identity?

Instrumentalisation (paragraph 8.3 -8.5)

Q4 Would the creation of a clone of a human person be an ethically unacceptable act?

Experimental human beings (paragraphs 8.6)

Q5 Would the likely cost in terms of failures and/or malformations inevitable in developing a programme of human reproductive cloning be ethically acceptable?

Natural/Unnatural (paragraph 8.7)

Q6 What ethical importance might be attached to the distinction between artificial processes for which there are parallels in natural processes and those for which there are not?

9.2 We will also be advising Ministers on ways to build public confidence in and understanding of new developments in genetic techniques. We would welcome any suggestions you may have on what this advice might be in respect of the implications of human cloning.

9.3 We are grateful to you for taking the time taken to read and respond to this consultation paper. Please send your replies, by 30 April 1998 to :

The HGAC Secretariat
c/o Office of Science and Technology
Albany House
94-98 Petty France
London SW1H 9ST

We may wish, in the future, to publish some of the views expressed in this paper or those arising from this consultation exercise. Should you wish your views to be treated in confidence, please make this clear in any paper you submit to us.

Further copies of this paper are available on request from Chris Hepworth (faxed requests preferred - FAX: 0171 271 2028)

This paper can also be located on our Web Site location: www.dti.gov.uk/hgac

ANNEX A

HGAC/HFEA CLONING WORKING GROUP

Terms of reference:

to consider the planning, drafting, distribution and analysis of a joint HGAC and HFEA consultation paper on the issues for human genetics arising from advances in mammalian cloning, and advise the HGAC and HFEA.

Membership

CHAIRMAN - Revd Dr John Polkinghorne KBE FRS
Chairman - Advisory Committee on Genetic Testing, HGAC member

Professor Christine Gosden
Professor of Medical Genetics, University of Liverpool, HFEA member

Dr Anne McLaren DBE FRS
Principal Research Associate, Wellcome/CRC Institute, HFEA member

Dr George Poste FRS
Chief Science & Technology Officer, SmithKline Beecham,, HGAC member

THE HUMAN GENETICS ADVISORY COMMISSION (HGAC)

The Human Genetics Advisory Commission (HGAC) was established in December 1996 to take a broad view of developments in human genetics and advise on ways to build public confidence in the application of the new science.

The terms of reference of the HGAC are to:

- keep under review scientific progress at the frontiers of human genetics and related fields;
- report on issues arising from new developments in human genetics that can be expected to have wider social, ethical and/or economic consequences, for example in relation to public health, insurance, patents and employment;
- advise on ways to build public confidence in, and understanding of, the new genetics.

Membership

HGAC is chaired by Professor Sir Colin Campbell. Other Members are: Professor Cairns Aitken, Dr Michaela Aldred, Professor Martin Bobrow, Mrs Doris Littlejohn, Dr Onora O'Neill, Dr George Poste and Ms Moira Stuart. Professor Norman Nevin and Rev Dr John Polkinghorne, the Chairmen of the Gene Therapy Advisory Committee and the Advisory Committee on Genetic Testing, respectively, are also members.

HUMAN FERTILISATION AND EMBRYOLOGY AUTHORITY (HFEA)

TERMS OF REFERENCE

The HFEA is a statutory body whose major function is to license all fertility treatments involving the use of embryos created outside the body (IVF) or donated eggs or sperm (e.g. donor insemination). The Authority also licenses the storage of eggs, sperm and embryos and all research on embryos.

The HFEA was established by the Human Fertilisation and Embryology Act 1990 and took up its powers on 1 August 1991. In addition to its licensing role, the HFEA has several other responsibilities including:

- to publish the Code of Practice giving guidance to centres on how they should carry out licensed activities;
- to keep a confidential register of information about donors, patients and treatments;
- to publicise its role and services which licensed centres provide;
- to give advice and information to licensed centres;
- to give information and advice to people seeking fertility treatment, to donors, to people who may need to store sperm, eggs or embryos for medical reasons and to the general public; and
- to keep the whole field of fertility treatment and research under review, whether the activities are licensed or not, and make recommendations to the government if asked to do so.

Membership

HFEA is chaired by Mrs Ruth Deech. Other members are: Dr Gulam Bahadur, Professor David Barlow, Professor Ruth Chambers, Mrs Jane Denton, Ms Liz Forgan, Professor Christine Gosden, David Greggains, Professor Andrew Grubb, Professor Martin Johnson, Richard Jones, Professor Stuart Lewis, Dr Brian Lieberman, Dr Anne McLaren, Dr Joan Stringer, Professor Allan Templeton, Professor Anthony Thiselton, Julia Tugendhat, John Williams.

Annex B

GLOSSARY

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.

Chromosomes: nucleic acid-protein structure in the nucleus of a cell. Chromosomes are composed chiefly of DNA, the carrier of hereditary information. Chromosomes contain genes, working lengths of DNA that carry the genetic code for specific proteins, interspersed with large amounts of DNA of unknown function. A normal human somatic cell contains 46 chromosomes; a normal human gamete cell contains 23 chromosomes.

Cloning: copying and propagation without altering the nuclear genome.

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

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".

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

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 an embryo after the eighth week of development until birth.

Gene: a working length of a chromosome composed of DNA. Each of the body's 100,000 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 cell all of whose surviving descendants will form sperm or eggs. All other body cells are known as "somatic" cells.

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

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

In Vitro Fertilisation (IVF): eggs and sperm are collected and put together to achieve fertilisation outside the body.

Mitochondria: cellular organelles that provide energy to the cell. The mitochondrion contains some of its own genes.

Monozygotic: formed from a single fertilised egg.

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

RNA: Ribonucleic acid

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

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

Therapeutic cloning: medical and scientific applications of cloning technology which do not result in the production of genetically identical fetuses or babies. These techniques may be undertaken to advance fundamental research and therefore not all such applications will lead to immediate therapeutic utility.

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

Zygote: the single-celled fertilised egg.

Annex C

EXPERIMENTS WHICH LED TO DOLLY AND SUBSEQUENT DEVELOPMENTS

The first evidence that it was possible to clone vertebrate animals using nuclear replacement was in 1952. The first series of experiments, using cells from tadpoles as the source of donor nuclei, produced adults but at a very low efficiency. Although the cells used were highly specialised, they were not derived from adult frogs, so the cells might not have been fully differentiated. Later, clones of tadpoles were obtained by nuclear transfer from differentiated adult frog skin cells to an enucleated egg establishing that differentiation of cells involving selective gene expression does not require the loss or irreversible inactivation of genes. No viable adult frog developed from these tadpoles.

In contrast, cloning by embryo splitting, from the 2-cell up to the blastocyst stage, has been extensively used in sheep and cattle to increase the yield of progeny from genetically high grade parents. Embryo splitting was first used to produce genetically identical sheep ten years ago at Cambridge. This technique has been used extensively in sheep since then. Because of the different pattern of early development, embryo splitting is much less successful in mice. From a scientific point of view, it would probably not be very effective in the human, although monozygotic (one-egg) twins and higher multiples occur naturally at a low incidence.

The Ministry of Agriculture, Fisheries and Food (MAFF), the Biotechnology and Biological Sciences Research Council (BBSRC), industry and the European Union have funded research at the Roslin Institute on the development of nuclear replacement technology since 1991 because of its potential to contribute towards genetic improvement of livestock. In announcing the birth of two genetically identical normal lambs (Megan and Morag) in 1996, the Roslin Institute reported a new method of cloning sheep embryos, which involved first establishing cell cultures from single embryos. Nuclei from the cultured cells were transferred to enucleated unfertilised sheep eggs, particular attention being paid to the cell cycle stage of both donor and host cells, and the eggs were then artificially stimulated to develop. More recently, in creating Dolly, the Roslin Institute transferred a nucleus from a cell culture of adult sheep cells.

Dolly appears to be the first and only example of an adult vertebrate which has been cloned from another adult. However, it has yet to be established whether the transferred nucleus was from a differentiated mammary gland cell or from a stem cell. It is not clear whether Dolly is normal or whether she could have subtle problems that might lead to serious diseases. Concern has been expressed that the use of an adult donor cell will have effects on ageing

and could perhaps lead to increased incidence of diseases such as cancer. Dolly appears to be a normal healthy animal and her development will continue to be closely monitored as she grows older.

There have also been major developments since Dolly's announcement. News of "Polly" was released by PPL Therapeutics in July 1997. This project is part of a PPL programme which aims to develop technology which will allow large amounts of proteins of therapeutic value to humans to be produced economically. In creating Polly, PPL for the first time combined existing techniques of nuclear replacement and transgenics. The nuclei in cultured fibroblast cells from a female sheep fetus were first modified through the addition of the human gene for factor IX (a blood clotting protein), by a process known as transfection. The modified nucleus was then introduced into the sheep's egg from which the DNA had been removed - the nuclear replacement step. In this way, Polly has been transgenically modified to enable her to produce therapeutic human proteins in her milk, and was created using nuclear replacement technology. The ability to clone transgenic sheep offers the prospect of the economically viable generation of flocks of sheep which are of particular benefit to humans.

Nuclear replacement has also been used for cloning in various mammalian species (mice, rabbits, cattle), but until recently only nuclei taken from very early embryos were effective, and development was often abnormal, for reasons that are not fully understood. Recently, in the United States, ABS Global Inc. have cloned a Holstein Bull, Gene, by transfer of a fibroblast nucleus from a male Holstein fetus. This was the first calf to be born from a non-embryo-derived cell.

Annex D

BRIEF DETAILS OF LAWS IN SOME OTHER COUNTRIES

Denmark

Act No. 503 on a Scientific ethical Committee System and the Handling of Biomedical Research Projects (1992)
Research on cloning (production of genetically identical individuals) is forbidden as is nuclear substitution.

Act No. 460 on Medically Assisted Procreation in connection with medical treatment, diagnosis and research (1997)
This confirms the Danish Parliament's position, of 25 January 1995, that treatment can not be initiated in areas where a research ban already exists under the 1992 Act.

Germany

Federal Embryo Protection Act 1990
The creation of an embryo genetically identical to another embryo, foetus or any living or dead person is an offence.

Norway

Law No 56 on the medical use of biotechnology 1994
Implicitly prohibiting embryo cloning.

Slovakia

1994 Health Care Law
Implicitly prohibiting embryo cloning.

Spain

Law No 35/1988 on Assisted Reproduction Procedures
Explicitly prohibiting embryo and oocyte cloning with criminal sanctions.

Sweden

Law No 115 14 March 1991
Implicitly prohibiting embryo and oocyte cloning with criminal sanctions.

Switzerland

Federal Constitution
Legally binding, implicitly prohibiting embryo cloning. If adopted, the **Federal Bill on Medically Assisted Procreation 1997** will explicitly prohibit embryo and oocyte cloning with criminal sanctions.

Countries which do not currently have any legislation relating to cloning: Greece, Ireland and the Netherlands.

These details were correct to the best of our knowledge at the time of publication.

Human Genetics Advisory Commission

Albany House 94-98 Petty France London SW1H 9ST
Telephone 0171 271 2131
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29 January 1998

Dear Colleague

CLONING ISSUES IN REPRODUCTION, SCIENCE AND MEDICINE

It was on the day of the HGAC's first meeting in 1997 that Scottish scientists told the world that they had cloned a sheep and called her Dolly. This scientific breakthrough captured the imagination of many throughout the world and we hear how it might open both the most wonderful and the most terrifying possibilities.

There is international concern that this technology might lead to the production of genetically identical human beings. However, the UK has effectively banned cloning for the deliberate creation of whole human beings under the Human Fertilisation and Embryology Act 1990.

It would seem that considerable confusion has been caused because the term "cloning" is used to describe a number of entirely different concepts. In the attached consultation paper, for the purposes of clarity, we use two distinct meanings: "human reproductive cloning", that is the production of genetically identical human beings, which is banned; and what may broadly be called "therapeutic cloning", which (although not coterminous with scientific usage) may be used to describe other applications of nuclear replacement technology, which do not involve the creation of genetically identical individuals.

The Commission and the Human Fertilisation and Embryology Authority will be advising Ministers later this year on the issues raised by cloning. To inform our views we decided to undertake a targeted consultation exercise. The attached paper raises a number of specific questions directed primarily to specialists drawn from organisations with scientific, legal, clinical and ethical interests. By publishing this consultation paper we hope to stimulate wider informed debate on this issue.

We would be very grateful for your comments on how the technology might actually develop, the opportunities and problems that would be raised by human reproductive cloning and other applications of nuclear replacement technology. We are also interested in your views on the priorities for the future and the ethical setting in which these scientific developments are taking place; including any additional ethical issues raised by human cloning that you have identified. In particular, we would welcome answers to the questions set out in Section 9. Please reply by 30 April 1998 to the HGAC Secretariat at the above address.

Sir Colin Campbell
HGAC Chairman

Ruth Deech
HFEA Chairman

Human Genetics Advisory Commission

PRESS NOTICE

29 January 1997

COMMISSION AND HFEA LAUNCH NATIONAL CONSULTATION

A consultation paper on the implications of human reproductive cloning and therapeutic cloning was published today by the Human Genetics Advisory Commission (HGAC) and the Human Fertilisation and Embryology Authority (HFEA).

Welcoming the publication of the consultation document, "Cloning Issues in Reproduction, Science and Medicine", the Chairman of the HGAC, Sir Colin Campbell, said:

"The announcement about Dolly the cloned sheep, in February 1997, captured the imagination of many throughout the world. We have been told that this breakthrough will open both wonderful and the most terrifying possibilities and people are understandably concerned about what the implications really are. It is important to sort out the scientific facts from the science fiction.

"Considerable confusion has been caused because the term 'cloning' is used to describe a number of entirely different concepts. It is important to distinguish between "reproductive cloning", where the intention is to produce identical individuals, and what may broadly be called "therapeutic cloning" which, for the purposes of clarity, may be used to describe techniques such as producing replacement skin, cartilage or bone tissue for treating victims of serious accidents or disease. The latter meaning also includes techniques which, although not therapeutic in themselves, may lead ultimately to therapeutic benefits."

Mrs Ruth Deech, Chairman of the HFEA, said:

"Human reproductive cloning is not permitted in the UK. However, there are potential benefits of research involving therapeutic cloning technology, where the end result will not involve creating genetically identical fetuses or babies."

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Press enquiries 0171 215 5377

"We are seeking views on how cloning technology might develop, the opportunities and problems raised and the ethical setting in which these scientific developments are taking place."

Sir Colin added:

"We would welcome opinions from a broad section of society and I invite all those who have an interest in this issue to share their views with us. We will consider the findings carefully before reporting to Ministers later this year."

Notes to Editors

1. The closing date for responses to this consultation paper is 30 April 1998. Copies are available on request from Chris Hepworth (Faxed requests preferred. Fax: 0171-271 2028 Tel: 0171-271 2064). The paper can also be found on the HGAC Website (www.dti.gov.uk/hgac).

2. The HGAC identified cloning as a priority at its first meeting on 27 February and, in view of the HFEA's responsibility for the licensing of human embryo research, the two organisations decided to work together to develop a consultation paper on cloning. The aim of the consultation is to elicit a full and open debate, to ensure that advice to Ministers on this subject is well founded and reflects the views of all those consulted.

3. A joint HGAC/HFEA Cloning Working Group (CWG), chaired by Reverend Dr John Polkinghorne (Chairman of the Advisory Committee on Genetic Testing and HGAC member), was established to take this issue forward. Other members of the group are Professor Christine Gosden (Professor of Medical Genetics at the University of Liverpool and HFEA member), Dr Anne McLaren (Principal Research Associate at the Wellcome/CRC Institute and HFEA member) and Dr George Poste (Chief Science and Technology Officer at SmithKline Beecham and HGAC member).

4. Cloning by nuclear transfer of an embryo is forbidden by the Human Fertilisation and Embryology Act 1990. Cloning by splitting embryos or the nuclear transfer of eggs may only be carried out with a licence from the Human Fertilisation and Embryology Authority. The Authority has decided not to license the use of cloning by the splitting of embryos or the nuclear transfer of eggs for treatment purposes, or for research directed towards cloning for treatment purposes.

HGAC Press Enquiries: 0171-215 5377/5962
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Textphone for those with hearing impairments: 0171-215 6740
Public Enquiries: 0171-215 5000
HFEA Press Enquiries: 0171 377 5077 Ext 205

P/98/067

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press notice

29 January 1998

MINISTER WELCOMES CONSULTATION ON CLONING ISSUES

A consultation paper on cloning issues in reproduction, science and medicine was published today by the Human Genetics Advisory Commission (HGAC) and the Human Fertilisation and Embryology Authority (HFEA).

Welcoming the paper, John Battle, Minister for Science, Energy and Industry said:

"The Government welcomes this initiative by the HGAC and HFEA. It is vital that there is open discussion of the issues raised by advances in biosciences to ensure that they are life-enhancing and understood by the public. We need to ensure that scientific and technological developments do not outstrip our moral capacities to handle them. We have to work on the science but also on our developing moral values. Recent developments offer significant opportunities to improve our quality of life, yet they can also raise wider questions for some people, for example on the ethics involved.

"If we are to gain the full advantage of these developments and an understanding of the balance of risks and benefits associated with them, it is important that bodies like the HGAC and HFEA, with the support of the Government, consider these questions by engaging in a full and open debate."

Notes for Editors

1. The aim of the consultation by HGAC and HFEA is to elicit a full and open debate, to provide them with sufficient underpinning material to ensure that the subsequent advice to Ministers on this subject is well founded and reflects the views of all those consulted/concerned.
2. A joint HGAC/HFEA Cloning Working Group (CWG), chaired by Reverend Dr John Polkinghorne (Chairman of the Advisory Committee on Genetic Testing and an HGAC member), has been established to take this issue forward. A separate press notice covers this (P/98/066).

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