DEPARTMENT OF HEALTH & HUMAN SERVICES

Program Support Center

Division of FOIA Services
Parklawn Bldg. Rm. 19-01
5600 Fishers Lane
Rockville MD 20857
PH: 301-492-4800
Fax: 301-492-4848

PSC Case No. : 14-0038

November 18, 2013

John Greenewald Jr
[redacted]

Dear Mr Greenewald:

This is in response to your September 24, 2013, Freedom of Information Act (FOIA) request sent to the Defense Technical Information Center (DTIC). You asked for a copy of document ADB249413, entitled, "Cloning Human Beings: Recent Scientific and Policy Ducuments."

DTIC forwarded your request to the Presidents Commission for the Study of Bioethical Issues (PCSBI). Please note that the PCSBI is not the custodian of the records.

DTIC erred in forwarding the request to the Department of Health and Human Services (HHS).

PCSBI advised us that the document was prepared for the National Bioethics Advisory Commission and their work is archived at http://bioethics.georgetown.edu/nbac/ which is hosted and maintained by the Bioethics Research Library at Georgetown University.

Sincerely,

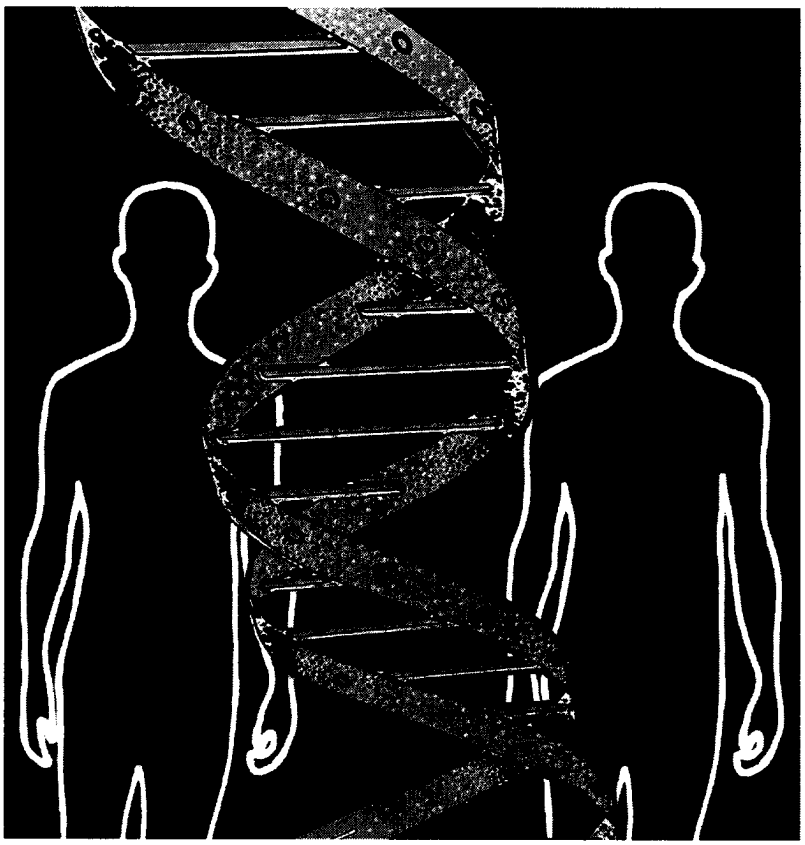
Glenn Voelker
Division of FOIA Services

RAND

Cloning Human Beings

Recent Scientific and Policy Developments

Elisa Eiseman



MR-1099.0-NBAC

August 1999

Prepared for the
National Bioethics Advisory Commission

Science and Technology Policy Institute

This is a final report of a project performed within RAND's Science and Technology Policy Institute.
It has been formally reviewed but has not been formally edited.

PREFACE

In response to the news of the cloning of Dolly, the first mammal to be cloned from an adult cell, President Clinton asked the National Bioethics Advisory Commission (NBAC) to report to him on the legal and ethical issues that cloning raises in regard to its potential use in human beings. On June 9, 1997, NBAC delivered its recommendations to the President. In their recommendations, NBAC agreed that the creation of a child by somatic cell nuclear transfer is scientifically and ethically objectionable at this time.

Since June 1997, when NBAC presented its report to the President, several developments have come to bear on this issue. Therefore, the purpose of this report is to provide an update on developments since June 1997. This update will include an overview of scientific developments in cloning (including both mammalian cloning and more basic research techniques), as well as proposed bills in Congress, current state legislation, and international policies on cloning. This update is intended to supplement, not replace, the more comprehensive assessment recommended by NBAC in their report *Cloning Human Beings* (NBAC, 1997).

This document was prepared for the National Bioethics Advisory Commission through RAND's Science and Technology Policy Institute. The information contained in this document is intended for inclusion in the NBAC's report on embryonic stem cell research for the President of the United States. In addition, this report may be used to inform the President of recent scientific and policy developments pertaining to the cloning of human beings.

Originally created by Congress in 1991 as the Critical Technologies Institute and renamed in 1998, the Science and Technology Policy Institute is a federally funded research and development center sponsored by the National Science Foundation and managed by RAND. The Institute's mission is to help improve public policy by conducting objective, independent research and analysis on policy issues that involve science and technology. To this end, the Institute

- Supports the Office of Science and Technology Policy and other Executive Branch agencies, offices, and councils
- Helps science and technology decisionmakers understand the likely consequences of their decisions and choose among alternative policies
- Helps improve understanding in both the public and private sectors of the ways in which science and technology can better serve national objectives.

Science and Technology Policy Institute research focuses on problems of science and technology policy that involve multiple agencies. In carrying out its mission the Institute consults broadly with representatives from private industry, institutions of higher education, and other nonprofit institutions.

Inquiries regarding the Science and Technology Policy Institute or this document may be directed to:

Bruce Don
Director, Science and Technology Policy Institute
RAND
1333 H St., N.W.
Washington, D.C. 20005

Phone: (202) 296-5000
Web: http://www.rand.org/centers/stpi/
Email: stpi@rand.org

CONTENTS

FIGURES

TABLES

SUMMARY

The birth of Dolly, the first mammal to be cloned from an adult cell, brought into sharp focus the future possibility of cloning human beings along with all its inherent moral, ethical and legal implications. In response to the news of the cloning of Dolly, President Clinton asked the National Bioethics Advisory Commission (NBAC) to report to him on the legal and ethical issues that cloning raises in regard to its potential use in human beings. On June 9, 1997, NBAC delivered its recommendations to the President. In their recommendations, NBAC agreed that the creation of a child by somatic cell nuclear transfer is scientifically and ethically objectionable at this time.

Since June 1997, when NBAC presented its report to the President, several developments have come to bear on this issue. There have been significant scientific advances in the field of somatic cell nuclear transfer. In addition, the policy responses to cloning of human beings have been intense. There has been legislative and regulatory action taken at the state, federal and international levels.

The cloning of Dolly has paved the way for major advances in biotechnology, reproductive medicine, and cellular-based transplantation therapies. In the last two years, since the cloning of Dolly, there have been several scientific advances. The ability to clone mammals other than sheep from adult cells has been reported for cows and mice. In addition, techniques have been developed to produce cloned animals carrying specific genes, providing an efficient means for producing genetically engineered animals that can make proteins in their the milk that could then be used for pharmaceutical or clinical purposes. The last cow of a rare breed has been cloned in an effort to save the breed from extinction, and scientists are preparing to clone other rare and endangered animals. Nuclear transfer technology has also been used for human applications, including in preimplantation diagnosis during in vitro fertilization, to try to treat infertility, and in an attempt to produce human embryonic stem cells. Many of these advances hold the promise of improved treatments for diseases for which there are currently no good alternatives.

Scientists are just beginning to explore the potential future uses of somatic cell nuclear transfer cloning. Before long, the preservation of genetically important strains and mutants of laboratory and farm animals, the preservation and propagation of rare and endangered species, and the unlimited multiplication of elite animals from selected matings will be routine. By combining cloning technology with transgenic techniques, the precise and efficient genetic modification of farm animals will be possible. By genetically engineering cloned animals to express human proteins (e.g. histocompatiliblity antigens) on the surface of cells and organs, the risk of immune rejection in xenotransplantation may be significantly reduced. In addition, cloning technology may lead to the development of customized (e.g. autologous) human embryonic stem cells for use as cell and tissue based therapies that would not be rejected by the patient's immune system.

While cloning techniques may one day provide improved treatments for diseases, revolutionize the production of biopharmaceuticals, and save endangered species, mammalian cloning does have its risks. In addition to high rates of spontaneous abortion late in pregnancy and death soon after birth, mammalian cloning has been linked to a developmental defect of the immune system and may be associated with premature aging. Thus, the question of safety remains, and casts doubt on the future uses of mammalian cloning.

Beyond the safety concerns, the prospect of cloning human beings raises several other ethical concerns. These concerns have prompted calls for worldwide bans. Consequently, language that directly prohibits the use of federal funds for cloning of human beings was included in appropriations legislation that prohibits the use of federal funds for human embryo research. There is also proposed federal legislation that would make it unlawful for anyone, whether in the public or private sector, to clone a human being. In addition, five states have enacted legislation prohibiting cloning of human beings. The FDA has also asserted its authority to regulate the cloning of human beings.

Similarly, several other nations and international organizations have also enacted laws or issued policy statements prohibiting the cloning of human beings. Argentina, Australia, Belgium, Canada, China, Denmark, France, Germany, Israel, Japan, Norway, Peru, Slovakia, South Korea, Spain, Sweden, Switzerland, and the United Kingdom already have laws or have announced plans to pass laws prohibiting the cloning of human beings. In addition, the Denver Summit of Eight, the Council of Europe, the World Health Organization (WHO), UNESCO's International Bioethics Committee (IBC), the European Commission, and the Human Genome Organization (HUGO) have called for a worldwide ban on the cloning of human beings.

It is clear that the potential benefits that may be realized through the use of cloning technology are many. However, the potential for cloning a child is an issue that we will be grappling with for a long time to come. Therefore, responsible public policy will need to be crafted in such a way as to prevent the use of cloning technology for purposes for which it is found to be ethically unacceptable, while allowing for beneficial uses that hold so much promise for curing human diseases.

ACKNOWLEDGMENTS

The author would like to thank Eric Meslin, Kathi Hanna and Harold Shapiro for their critical reading of this manuscript. She would also like to thank Lori Knowles, from the Hastings Center, and Anna Slomovic, from RAND, for their in depth reviews and insightful comments of this manuscript. Finally, she would like to acknowledge the usefulness of the Pharmaceutical Research and Manufacturers of America (PhRMA), Cloning Legislation and Regulation website for current information on state and federal legislation pertaining to the cloning of human beings (http://www.phrma.org/genomics/cloning/legislation.html).

GLOSSARY

Word	Definition
blastocyst	1) stage in development of a mammalian embryo; 2) stage of development resulting from first specialization event occurring around 6-7 days after fertilization, just before the zygote attaches to the uterus; 3) structure of approximately 100 cells consisting of an outer layer of trophoblast surrounding an inner cell mass.
blastocyst division	performed by dividing a blastocyst into two so that each part receives an approximately equal number of cells. Each blastocyst is then transferred to the uterus, so that, at most, one blastocyst gives rise to identical twins.
blastomere separation	involves the dissociation of a two- to eight-cell zygote and then culturing the cells individually. Once the cells have divided a few times, they spontaneously form smaller than normal embryos, which can be transferred to the uterus.
cloning	1) to produce a copy; 2) the production of a precise genetic copy of a molecule (including DNA), cell, tissue, plant, or animal; 3) a form of asexual reproduction.
cumulus cells	cells that nourish eggs in the ovaries of females.
differentiate	the process by which cells become specialized in their structure and function
ectogenesis	Developing an embryo or embryonic tissue in vitro, or within an artificial environment.
embryo	1) the young of any organism in the early stages of development; 2) stage in prenatal development of a mammal between the ovum and the fetus; 3) in humans, stage of development between the 2nd and 8th weeks inclusive.
extracorporeal	outside of, or unrelated to, the body.
fetus	1) the latter stages of the developing young; 2) in humans, from week 9 of development until the time of birth.
fibroblast	a cell of the connective tissue capable of forming elastin and collagen fibers.
gamete	1) any germ cell, whether ovum or spermatozoon; 2) a mature male or female reproductive cell.
germ cells	gametes or the cells that give rise directly to gametes.
mitochondria	1) an organelle found in the cell cytoplasm; 2) the principal energy source of the cell.

nuclear transfer	the transfer of a nucleus from an embryonic, fetal or somatic cell into an enucleated egg to produce an organism identical to the cell donor.
oocyte	1) a diploid cell that will undergo meiosis (a type of cell division of germ cells) to form an egg; 2) immature ovum.
ovum	1) female sex cell; 2) female reproductive or germ cell.
quiescent	marked by a state of inactivity or repose.
somatic cells	[from *soma* - the body] 1) cells of which in mammals and flowering plants normally have 2 sets of chromosomes, one derived from each parent; 2) all cells of an organism with the exception of the germ cells.
somatic cell nuclear transfer	1) the transfer of a nucleus from a somatic cell into an enucleated oocyte; 2) technique used to clone adult animals.
transgenic animal	1) an animal in which there has been a deliberate modification of the genome - the material responsible for inherited characteristics; 2) an animal that has foreign DNA integrated in its germ line as a result of the experimental introduction of DNA; 3) genetically-engineered animal.
zygote	1) the cell resulting from the fusion of two gametes in sexual reproduction; 2) a fertilized egg (ovum); 3) the diploid cell resulting from the union of a sperm and ovum; 4) the developing entity during the first week after fertilization

LIST OF SYMBOLS

Symbol	Definition
AHEC	Australian Health Ethics Committee
AIDS	Acquired Immunodeficiency Syndrome
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic Acid
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
HFEA	Human Fertilisation and Embryology Authority
HGAC	Human Genetics Advisory Commission
HUGO	Human Genome Organization
IBC	UNESCO's International Bioethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
IVF	In vitro fertilization
NBAC	National Bioethics Advisory Commission
NHMRC	National Health and Medical Research Council
PHSA	Public Health Service Act
UNESCO	United Nations Economic, Scientific and Cultural Organisation
WHO	World Health Organization

BACKGROUND

Cloning, which literally means to make a copy, is the asexual reproduction of a precise genetic copy of a molecule, cell, tissue, plant, or animal. However, scientists use the word "cloning" in many different ways. Molecular cloning refers to the copying of DNA fragments. For example, the human gene for insulin has been cloned into bacteria to produce insulin for the treatment of diabetes. In addition, human cells are routinely cloned to study cancer or genetic diseases. These types of cloning are integral tools in biotechnology, and have been used to produce breakthrough medicines, diagnostics and vaccines to treat heart attacks, cancer, diabetes, hepatitis, cystic fibrosis and many other diseases.

The cloning of animals was originally conceived of as a way to understand the genetic processes that regulate development and differentiation. As cloning technology has progressed and the prospect of producing large numbers of genetically identical animals has increased, proposals for applications of animal cloning in areas beyond basic developmental biology have abounded. It has been proposed that animal cloning could be useful for the preservation and multiplication of genetically important animals, the preservation and propagation of rare and endangered species, and reducing the number of animals required in experiments. Beyond these reproductive applications lay numerous therapeutic uses of animal cloning technology, including the production of transgenic animals that can produce therapeutic proteins in their milk, and the development of human embryonic stem cells for use as cell and tissue based therapies.

There are currently several techniques available to clone animals including blastocyst division, blastomere separation, and nuclear transfer. It is important to note, however, that nuclear transfer is the only technique that allows for somatic cell cloning from adult cells. In addition, nuclear transfer is the only technology that offers the possibility of cloning large numbers of genetically identical animals.[1]

Nuclear transfer entails placing the nucleus from an embryonic, fetal or somatic cell in an enucleated egg (an egg from which the nucleus containing the genetic material has been removed). In some cases, this is achieved by injecting an isolated nucleus into the enucleated egg, but in other experiments it is achieved by placing a single cell next to the enucleated egg and fusing the two membranes together artificially. The nucleus from the cell then enters the egg cytoplasm and directs the development of the embryo. Somatic cell nuclear transfer, the technique used to clone the Scottish mountain sheep, Dolly, from an udder cell of an adult ewe, entails fusing a somatic cell with an enucleated egg.

---

[1] Blastocyst division or induced twinning is performed by dividing a blastocyst into two so that, at most, one blastocyst gives rise to identical twins. Blastomere separation involves dissociation of a two- to eight-cell zygote yielding, at most, eight genetically identical animals.

Nuclear transfer is not new technology. Nuclear transfer experiments were first performed in amphibians in the 1952, and then in mammals in the 1980s to answer the question of whether the genetic material of differentiated (specialized) cells from adult animals is irreversibly modified (reviewed in First and Prather, 1991). In these experiments, animals could be cloned successfully only when nuclei from embryos were used, and none were cloned from nuclei of adult animals. The conclusions derived from these early experiments were that as cells become more differentiated, their nuclei become less capable of undergoing developmental reprogramming, and therefore, somatic cell nuclear transfer cloning from adult cells may not be possible.

The nuclear transfer technology that produced Dolly was not new to Ian Wilmut and his group in Scotland, either. They began studying the control of cell development over ten years ago, and had already published a report of the first mammal to be cloned from established cell lines derived from sheep embryos (Campbell et al., 1996). This earlier work established that donor cells, induced to exit the growth phase and become quiescent before being used for nuclear transfer, were more susceptible to re-programming by the recipient egg cell and resulted in the normal development and birth of cloned offspring (Campbell et al., 1996). What was new about Dolly was that she was the first mammal to ever be cloned from an adult cell (Wilmut et al., 1997). For the first time, it was possible to use the genetic material from a single adult mammalian cell to develop a new individual mammal. Dolly provided the first evidence that fully differentiated somatic cells of an adult retain all the genetic information found in the early embryo, and that differentiation is a reversible process.

The announcement about the birth of Dolly brought into sharp focus the future possibility of cloning human beings along with all its inherent moral, ethical and legal implications. On February 24, 1997, President Clinton asked the National Bioethics Advisory Commission (NBAC) to deliver a report to him within 90 days on the legal and ethical issues involved in the cloning of human beings and "possible federal actions to prevent its abuse." On March 4, 1997, President Clinton imposed a ban on the use of federal funds for cloning human beings and asked for a voluntary moratorium by researchers funded by private sources.

On June 9, 1997, NBAC delivered its recommendations to the President. NBAC agreed that the creation of a child by somatic cell nuclear transfer is scientifically and ethically objectionable at this time because: 1) the efficiency of nuclear transfer is so low and the chance of abnormal offspring so high that experimentation of this sort in humans was premature; and 2) the cloning of an already existing human being may have a negative impact on issues of personal and social well being such as family relationships, identity and individuality, religious beliefs, and expectations of sameness. NBAC recommended a continuation of both the moratorium on the use of federal funding in support of any attempt to create a child by somatic cell nuclear transfer, as well as the voluntary moratorium for the private and non-federally funded sectors. NBAC further recommended that federal legislation be enacted to prohibit anyone from attempting, whether in a research or clinical setting, to create a child through somatic cell nuclear transfer cloning. However, such legislation should include a sunset clause to ensure that Congress reviews

the issue after a specified time period (three to five years) in order to decide whether the prohibition continues to be needed. In addition, any such regulatory or legislative actions undertaken to prohibit the creation of a child by somatic cell nuclear transfer should be carefully written so as not to interfere with other important areas of scientific research, such as the cloning of human DNA sequences and cell lines, neither of which raises the scientific and ethical issues that would arise from an attempt to create a child through somatic cell nuclear transfer.

Since June 1997, when NBAC presented its report to the President, several developments have come to bear on this issue, including:

- the introduction and passage of some state legislation related to cloning:
- the introduction of several bills in the Congress related to cloning;
- the announcements that several generations of mice were cloned from adult cells in Hawaii and 8 calves were cloned from a single adult cow in Japan;
- the development of statements and other guidelines by international organizations (including UNESCO and the Council of Europe); and
- sporadic attention by the public and the media to the acceptability of somatic cell nuclear transfer cloning for the purpose of creating a human being.

Therefore, the purpose of this report is to provide an update on developments since June 1997. This update will include an overview of scientific developments in cloning (including both mammalian cloning and more basic research techniques), as well as proposed bills in Congress, current state legislation, and international policies on cloning. This update is intended to supplement, not replace, the more comprehensive assessment recommended by NBAC in their report *Cloning Human Beings* (NBAC, 1997).

SCIENTIFIC UPDATE

The news of the cloning of the first mammal from an adult was met with great skepticism in the scientific community. It was not until other adult mammals had been cloned along with additional proof that Dolly was truly cloned from the udder cell of an adult sheep that scientists believed that cloning of adults was possible. The research that finally convinced scientists that cloning of adult animals was a reality includes the birth of 50 cloned mice and 8 cloned calves through somatic cell nuclear transfer. The potential utility of this technology was demonstrated when a rare breed of cattle was rescued from extinction by cloning the only surviving cow of the breed.

These significant advancements in cloning represent the utility of cloning for reproductive purposes. However, the fundamental techniques used in somatic cell nuclear transfer are also applicable to the development of novel therapeutics. For example, nuclear transfer technology has been used to produce transgenic cloned animals that make pharmacologically useful proteins in their milk, for preimplantation diagnosis during in vitro fertilization (IVF), to try to treat infertility, and in an attempt to produce human embryonic stem cells. These accomplishments in combination with scientific advancements in the use of cloning for reproductive purposes illustrate the great potential of somatic cell nuclear transfer. However, mammalian cloning is not fool-proof. In addition to high rates of spontaneous abortions late in pregnancy and death soon after birth, mammalian cloning has been linked to a developmental defect of the immune system and may be associated with premature aging. The scientific milestones achieved since the cloning of Dolly are outlined below and depicted in chronological order in Figure 1.

News about Dolly

Dolly, the Finn Dorset sheep born on July 5, 1996, was the first mammal ever cloned from an adult somatic cell (Wilmut, et al., 1997). Dolly was cloned from the udder of a pregnant six year old Finn Dorset ewe. The mammary cells from the udder were cultured in the laboratory before being used to create Dolly. The technique used to clone Dolly involved the fusion of an enucleated egg with a cultured mammary cell by using an electrical shock. The key to success at the Roslin Institute seems to have been that the mammary cells were starved (placed in medium containing few nutrients) for five days before being fused with the enucleated eggs. This placed the cells in a quiescent phase of their division cycle and may have made their chromosomes more susceptible to being reprogrammed to initiate the growth of a new organism after they were transferred into eggs. Even with this improvement, it took 434 oocytes to obtain 277 fusions out of which only 29 viable embryos resulted (Wilmut, et al., 1997). These embryos were implanted into surrogate Blackface ewes and only one gave birth to Dolly. Thus the cloning of adult mammals using this technique was a very inefficient process.

Proof that Dolly was Cloned from a Somatic Cell

Because Dolly was the one and only lamb born out of 277 fusions, one of the cornerstones of the scientific method had not been met — that of reproducibility. This led to a lot of skepticism in the scientific community about whether Dolly was really the clone of an adult animal. Two prominent biologists, Vittorio Sgaramella from the University of Calabria in Cosenza, Italy, and Norton Zinder of Rockefeller University in New York City, wrote a letter to the editor of the journal *Science*, asking for more convincing evidence that the experiment that produced Dolly worked as claimed (Sgaramella and Zinder, 1998). Zinder and Sgaramella ask several questions, including whether Dolly was really cloned from a mammary cell, one of the donor's rare stem cells, or from a contaminating fetal cell present in the udder of the pregnant donor ewe, and whether Dolly's DNA has mutations and other changes expected in an adult (Sgaramella and Zinder, 1998). Their main concern was that, at the time they wrote their letter, no one had reproduced Wilmut's results.

In response, Ian Wilmut's group and Alec Jeffreys' group, an independent group from the University of Leicester, set out to definitively answer Sgaramella's and Zinder's questions. They used DNA microsatellite analysis and DNA fingerprinting to compare nuclear DNA from the original piece of udder, frozen at the Hannah Research Institute, to the nuclear DNA of the cultured mammary cells that were used to create Dolly, to the nuclear DNA of Dolly, and subsequently found that all of the nuclear DNA sequences were identical (Ashworth, et al., 1998; Singer, et al., 1998). These data confirmed that Dolly was a clone derived from the mammary tissue of the six-year-old Finn Dorset ewe. These data also ruled out the possibility that Dolly could have come from a contaminating fetal cell present in the udder of the pregnant donor ewe. In addition, there was finally evidence to confirm that it was possible to clone mammals from adult cells. In the same issue of the journal *Nature*, in which the proof of Dolly's origins are published, scientists at the University of Honolulu in Hawaii reported the successful cloning of mice from the nuclei of adult cells (see below; Wakayama et al., 1998).

However, it appears that Dolly is not an exact genetic duplicate of the sheep that donated the mammary cell from which she was cloned. Scientists have tested the mitochondrial DNA from Dolly and nine nuclear transfer-derived sheep generated from fetal cells to determine the origins of their mitochondrial DNA. Mitochondria contain DNA that codes for 37 genes that control almost all of the energy metabolism in cells (Tanne, 1999). Mitochondrial DNA was analyzed in the blood, muscle, milk or placenta, and in all ten sheep was found to be derived solely from the enucleated egg with no contribution by the somatic or fetal donor cells (Evans et al., 1999). It was concluded that while all ten sheep were authentic nuclear transfer clones, they were actually genetic chimeras, containing somatic or fetal cell-derived nuclear DNA and oocyte-derived mitochondrial DNA (Evans et al., 1999). These results suggest that diseases caused by faulty mitochondrial genes may be prevented by using nuclear transfer technology to fuse the nuclear DNA from a diseased embryo with an oocyte that contains healthy mitochondria (Evans et al., 1999).

Dolly Gives Birth

Another question that was asked about Dolly was whether or not she was fertile and would be able to have offspring. This question was answered when Dolly was mated naturally with a Welsh mountain ram named David and gave birth to Bonnie on April 13, 1998 (Lederer, 1998). The birth of her lamb confirmed that Dolly was able to breed normally and produce healthy offspring. Almost 12 months later on April 1, 1999, it was reported that Dolly gave birth to healthy triplets, two males and one female (Associated Press, 1999). The ram David was also the father of these three lambs. The birth of these three lambs is further evidence that Dolly is able to breed normally.

Cloning of Other Mammals

Within days of the news of Dolly, there was a report about the cloning of rhesus monkeys from embryonic cells, representing the first successful cloning of primates (Henahan, 1997). Soon after, there was a report that a cow had been cloned from fetal cells (Holden, 1997). Even though both of these results represent significant achievements in the field of animal cloning, neither is an example of cloning of an adult animal.

The next documented proof of the cloning of adult mammal by somatic cell nuclear transfer came from a group at the University of Hawaii who reported the birth of cloned mice from cumulus cells, cells that nourish eggs in the ovaries of females (Wakayama, et al., 1998). A few months later, a group in Japan reported the birth of eight calves cloned by somatic cell nuclear transfer using cumulus cells and oviductal epithelial cells of adult female cows (Kato, 1998). In addition, scientists attempted the first inter-species cloning (Hotz, 1998). Nuclei from ear cells of five different species, sheep, pigs, rats, cattle and rhesus monkeys, were transplanted into enucleated cow eggs and developed into embryos, however none of them produced a successful pregnancy. Towards the end of 1998, two fertility specialists in South Korea claimed to have cloned a human embryo using an ovarian cell from a woman in her thirties by using the same technique that scientists in Hawaii used to clone mice (Weiss, 1998a). Recently, the first males to be cloned from adult cells were reported (Wakayama and Yanagimachi, 1999). In a span of three years, we have gone from the birth of a single cloned sheep to the existence of numerous cloned mice and cows, and claims of cloned human embryos. These advances in mammalian cloning are detailed below.

Neti and Ditto - Cloned Rhesus Monkeys

Just days after the announcement of the cloning of Dolly, scientists at the Oregon Regional Primate Research Center announced at a press conference the first nuclear transfer in primates, the cloning of two Rhesus monkeys using IVF-produced embryos as the source of donor nuclei (Henahan, 1997). The cloned monkeys, a male named Ditto and a female named Neti, were developed using cells from different embryos, so they are not genetically identical to each other (Meng et al., 1997). The research was funded by the National Institutes of Health National Center for Research Resources and the National Institute for Child Health and Human

Development. The ability to produce identical monkeys will allow for research on diseases such as AIDS, heart disease, and cancer that is more accurate, less expensive, and requires fewer animals.

Researchers at the Oregon Regional Primate Research Center have also been trying to clone monkeys from adult somatic cells. However, they have been unsuccessful despite 135 attempts (Weiss, 1999). Using a technique similar to the one used to create Dolly, the Oregon researchers were able to successfully fuse 75 percent of the donor cells with enucleated eggs, and 75 percent of these began to divide (Weiss, 1999). However, after transferring 135 embryos into 23 surrogate mothers, they did not achieve a single pregnancy (Weiss, 1999).

Gene - A Cloned Calf

Gene, a male Holstein calf, was cloned by ABS Global, an animal breeding company in DeForest, Wisconsin. The method used to create Gene differed from that used to create Dolly. Cultured cells from a 30-day-old fetus were initially fused with an enucleated egg. After the embryo began dividing, a cell was removed and fused with another enucleated egg. The resulting embryo was then implanted in a female cow to gestate. Gene, born in February of 1997, is the first cow to be cloned from cells that were growing in culture for a long time (Holden, 1997).

Cow Eggs Used to Clone Five Species

On Monday, January 19, 1998, at a meeting of the International Embryo Transfer Society, scientists at the University of Wisconsin-Madison announced that they had cloned five different species, including sheep, pigs, rats, cattle and rhesus monkeys, by transplanting the nucleus of a cell from the ear of adult animals into enucleated cows' egg (Hotz, 1998). The resulting embryos appeared to be guided by the genetic programming of the new nucleus, since a rodent nucleus produced a rodent embryo and a monkey nucleus produced a monkey embryo (Hotz, 1998). So far, however, all of the pregnancies have resulted in miscarriages. The research was conducted in the laboratory of Neal First who, a decade ago, was the first to make mammalian clones using undifferentiated embryonic cells from cattle.

The objective of the research was to determine whether the cytoplasm of a cow's egg could reprogram the genetic material of differentiated cells from an array of mammals. The development of embryos of several different animals suggests that the molecular machinery responsible for programming genes within the cytoplasm of the egg may be similar in all mammals. However, no one knows whether this technique could ever produce live offspring. The mitochondrial genes involved in energy metabolism that are left behind in the cytoplasm of the cow eggs after the nucleus is removed may be clashing with genetic information contained in the nuclei from the other species making it difficult for any resulting embryo to survive to term (Weiss, 1998b).

If the technical difficulties can be overcome, a practical use of the Wisconsin study is that cow eggs may serve as a convenient, universal recipient for the genetic material of other animals, including those animals where eggs may be difficult or impossible to obtain, such as endangered species or prized farm animals. In addition, if the technology is perfected, it could lead to the development of embryonic stem cell lines for the development of tissue for human transplants. By taking tissue from a transplant candidate and growing genetically identical tissue, problems of organ or graft rejection could potentially be eliminated. However, it is unclear whether this technique will be a feasible technique for creating transplantable tissue. If mitochondria from the cow egg remain, there may be problems with these cow-human hybrids. Unless it is possible to remove the cow mitochondria and replace them with human mitochondria, it may not be possible to overcome these problems.

Hawaiian Scientists Clone 50 Mice

In the July 23, 1998 issue of *Nature*, scientists from Hawaii reported that 22 healthy, fertile female mice had been cloned from the nuclei of adult ovarian cumulus cells, marking the first documented cloning of adult mammals since researchers in Scotland announced the birth of Dolly (Wakayama et al., 1998). The technique used was very similar to that used to produce Dolly, with three key exceptions: 1) instead of fusing a whole somatic cell with an enucleated egg, only the nucleus from the somatic cell was injected, reducing the amount of somatic cell cytoplasm introduced into the enucleated oocyte; 2) instead of using electric shocks to activate the reconstituted egg, chemicals (strontium and cytochalasin B) were used to start cell division; and 3) the hybrid cells were allowed to sit for up to six hours before stimulating them to start dividing, which caused chromosome condensation and may have facilitated the nuclear changes necessary for reprogramming (Wakayama et al., 1998). The first resulting cloned mouse to survive to adulthood, named Cumulina, was born on October 3, 1997. The success rate was low, with only 2 percent to 2.8 percent of the cloned embryos developing to term, but still represents an improvement over the technique used to produce Dolly, which only yielded one sheep out of 277 attempts. However, the mice that did survive seemed to be perfectly normal, have been mated, and have raised normal offspring of their own. Wakayama et al. were also able to take cells from the cloned mice and derive new clones (clones of clones) (Wakayama et al., 1998). In all, the group form the University of Hawaii have produced three generations of identical mice for a total of 50 clones (Lemonick, 1998).

This new ability to clone adult mice will allow scientists to better determine the technical and biological factors that contribute to the success of this type of cloning. Developmental biologists will also be able to address the crucial question of how the donor nucleus from a specialized cell becomes reprogrammed by the egg cytoplasm to enable it once again to give rise to all the different cell types in the animal body. In addition, scientists will be able to study the process by which genes turn on and off, and how cells become specialized for particular jobs in the body. Since both cancer and the aging process involve genetic changes at the cellular level, a better understanding of how genes work might have implications for anti-cancer and anti-aging treatment. By knowing what makes a liver cell a liver cell and a nerve cell a nerve cell, it may also

be possible one day to replace damaged or diseased cells in the body. Furthermore, in depth knowledge of mouse genetics and the short gestation period of mice (two and a half months), combined with the low cost of working with mice, will advance research into mammalian cloning much faster than has been possible in sheep and cattle.

Fibro - the First Male Mammal Cloned from an Adult Somatic Cell

Two of the scientists from Hawaii that cloned the adult female mice have also successfully cloned the first adult male animal, a mouse named Fibro (Wakayama and Yanagimachi, 1999). The scientists used fibroblast cells (for which the mouse is named) from the tails of adult male mice, and injected nuclei from these cells into enucleated mouse oocytes (Wakayama and Yanagimachi, 1999). Only 3 of the 274 embryos transferred to surrogate mothers reached full term (Wakayama and Yanagimachi, 1999). However, two of the offspring died within one hour after cesarean section due to respiratory failure, and only one male survived to become a fertile adult (Wakayama and Yanagimachi, 1999). Before the birth of Fibro, all of the reported clones of adult animals had been produced using cells derived from the female reproductive system, including mammary gland cells, ovarian cumulus cells, and oviductal cells. The cloning of an adult male mouse from fibroblasts demonstrates that cloning using adult somatic cells is not restricted to females or cells taken from the reproductive system, allowing for the preservation of valuable animals of either sex.

Japan Announces Cloned Calves

In the December 11, 1998 issue of the journal *Science*, scientists at Kinki University in Nara, Japan report the cloning of eight calves, from the cells of a single adult cow, using the same technique originally developed to produce Dolly the sheep (Kato, 1998). Cumulus cells and oviductal epithelial cells were obtained from a slaughter house from a single cow, cultured for several passages, and then made quiescent before being used for nuclear transfer. Six blastocysts derived from cumulus cells were transferred into three females, and four from oviductal cells were placed into two females. All five females became pregnant. Of the ten blastocysts transferred to cows, eight cloned female calves were born. However, four of the eight calves died soon after birth from "environmental causes" (Kato, 1998). Postmortem analysis revealed no abnormalities (Kato, 1998). This is not the first report of a cow cloned from adult cells. As noted below, New Zealand scientists said in August that they had made a calf from a single cell taken from the last remaining cow of a rare breed, and five other Japanese groups have claimed to have made clones of adult cows (Weiss, 1998c). This, however, is the first scientifically documented report of the cloning of cows from an adult cells, and may represent an efficient way to expand herds of valuable cows that have proven to be prize milk or beef producers, or cows that have been genetically engineered to make human medicines in their milk (Weiss, 1998c).

Korean Researchers Report Creation of Cloned Human Embryos

On December 14, 1998, Lee Bo-yon, a fertility specialist at Kyunghee University Hospital in Seoul, South Korea, and his colleague, Kim Sung-bo claimed to have cloned a human embryo using an ovarian cell from a woman in her thirties by using the same technique that scientists in Hawaii used to clone mice (Weiss, 1998a). They allowed the embryo to divide twice, into four cells, before stopping the experiment to abide by a 1993 national ban that prohibits research on more fully developed embryos. Although, the team cultured six eggs on two different occasions from two different women, only one developed into an embryo (WuDunn, 1998). The scientists' stated reason for pursuing this line of research was not to clone a human being, but rather to grow replacement organs. However, their research has not been confirmed or reviewed by other scientists. Furthermore, several scientists have voiced skepticism about these claims, pointing out that it is common for ordinary unfertilized eggs to divide twice if stimulated (Baker, 1999).

Cloning of Endangered Species

The preservation of rare and endangered species is an ongoing effort. Scientists have tried all the methods in their arsenals to increase the numbers of animals belonging to endangered species, including artificial insemination and in vitro fertilization, and now there may be a new technique available, somatic cell nuclear transfer. Scientists in New Zealand have used somatic cell nuclear transfer to clone the only surviving cow of a rare breed, and scientists in China have plans to clone the endangered panda. Even though making replicas of existing animals may expand the numbers of a dwindling species, it may, at the same time, limit the gene pool. Therefore, measures must be taken to ensure genetic diversity, such as breeding cloned animals with remaining wild ones.

New Zealand Scientists Clone Last Cow of Rare Breed

Scientists in New Zealand reported that they had cloned the lone surviving member of a rare breed of cow, marking the first cloning of a rare or endangered species (Weiss, 1998d). Lady, the only surviving cow of a herd that lived in isolation on Enderby Island, one of the barren sub-antarctic Auckland Islands, was cloned by scientists at the Ruakur Research Center in Hamilton, New Zealand. In 1992, the New Zealand government ordered that the herd be destroyed because it was disrupting the island's ecological balance. Only Lady was saved and brought back to the New Zealand mainland along with the semen from 10 killed bulls. As Lady advanced in age and with only one son created by in vitro fertilization, the scientists turned to somatic cell nuclear transfer cloning as a last resort. In collaboration with the New Zealand Rare Breeds Conservation Society, granulosa cells were retrieved from Lady's ovaries and fused with enucleated eggs from cows of different breeds. The developing embryos were implanted into the uterus of a surrogate Angus cow. On July 31, 1998, the first clone, named Elsie (a phonetic play on L.C. for "Lady's Clone") was born by Cesarean section (Weiss, 1998d). DNA fingerprinting tests proved that Elsie is genetically identical to Lady. Ten additional clones of Lady have also been created and

scientists hope that by inseminating them with sperm originally retrieved from the ten bulls, some diversity can be persevered in the herd (Newswire, 1998).

Cloning of the Endangered Panda

With only about 1,000 left in the world, pandas are quickly becoming extinct, mainly because of their quickly disappearing habitat, the high-altitude bamboo forests of the Sichuan and Gansu provinces. Furthermore, the intrusion of loggers has isolated panda communities from each other and diminished the number of available mates. Scientists are trying to prolong the pandas' existence by breeding them in captivity, using artificial insemination, and even creating test tube babies from eggs of a dead panda (Farley, 1998).

In an effort to save its panda population, Chen Dayuan, an embryologist at the Institute of Zoology of the Chinese Academy of Sciences, has turned to somatic cell nuclear transfer cloning to save the endangered species (Farley, 1998). A patch of skin taken from the belly of a panda during an unrelated operation will provide the cells for cloning. Because of objections to using the rare panda as experimental animals, Chen is attempting a trans-species cloning, in which a panda embryo will be implanted into a surrogate mother of another species, such as a black bear. There is also interest in the United States, where scientists have said that they would also like to try cloning pandas in a similar fashion.

Cloned Transgenic Animals

Since the middle of the 1980s, transgenic livestock have been produced by microinjecting DNA directly into fertilized oocytes. However, this technique has several drawbacks, including low levels of transgene integration, highly variable levels of expression and germline transmission, and a lag time of up to three years to generate a production flock. Somatic cell nuclear transfer offers a new way to efficiently produce transgenic animals. So far, the birth of transgenic lambs (Schnieke, et al., 1997), calves (Cibelli, 1998), and goats (Baguisi, et al., 1999) has been reported. These breakthroughs suggest that somatic cell nuclear transfer has the potential to become an important commercial strategy for creating transgenic animals to produce biopharmaceuticals.

Polly and Molly - Transgenic Sheep

The lambs Molly and Polly differ from Dolly in two ways: 1) they were cloned from the cells of 35-day-old sheep fetuses, not an adult animal; and 2) they were genetically engineered to carry both a human gene, human coagulation factor IX, and a marker gene for resistance to the antibiotic neomycin (Schnieke, et al., 1997). The birth of five genetically engineered lambs, cloned by a team led by Ian Wilmut at the Roslin Institute of Edinburgh, Scotland, and joined by team members from the Scottish biotechnology company PPL Therapeutics, was announced on July 24, 1997. Somatic cells can therefore be subjected to genetic manipulation in vitro and produce viable animals by nuclear transfer.

One of the transgenic clones, Polly, has already proven to have the human gene in her cells (Pennisi, 1997). However, it still remains to be seen if the transgenic sheep will produce useful quantities of factor IX, a protein that helps blood clot, in their milk. It is hoped that factor IX could be extracted from the milk and used to treat patients with hemophilia, an inherited bleeding disorder in which the blood lacks the ability to clot.

Other techniques have been used to develop drugs that can be produced in the milk of genetically engineered sheep or goats for the treatment of cystic fibrosis and heart attacks. These animals, however, were produced by injecting genes into a fertilized egg (pronuclear microinjection) and then implanting the egg in a surrogate mother, a technique less efficient than the cloning technique used to create Polly and Molly. Only about 2 percent of such microinjected eggs grow to live animals and only a small percentage of the survivors actually contain the target genes. Production of transgenic sheep by nuclear transfer requires fewer than half the animals needed for pronuclear microinjection. Therefore, the use of nuclear transfer coupled with genetic engineering represents a step toward achieving more efficient production of proteins for pharmaceutical or clinical use.

George and Charlie - Transgenic Cows

Three healthy, identical, genetically engineered calves were successfully cloned from a 55-day-old male fetus (Cibelli, 1998). The male calves were created through a combination of cloning and genetic engineering by a team led by James Robl at the University of Massachusetts and Steven Stice of Advanced Cell Technology, Inc. Two of these transgenic calves, named George and Charlie, were originally introduced at a meeting of the International Embryo Transfer Society on January 20, 1998 (Fitzgerald, 1998). All three calves contain two genetic alterations : 1) a marker gene (β-galactosidase); and 2) a gene that makes cells resistant to the antibiotic neomycin (Cibelli, 1998). The genes were detected in almost every tissue tested, including blood, spleen, and bone (Fitzgerald, 1998).

This accomplishment could lead to the mass production of drugs for humans in cows' milk. With previous microinjection techniques, about 500 embryos would have to be injected and transferred to recipient cows to get one transgenic offspring (Cibelli, 1998). Using the nuclear transfer technique with transgenic somatic cells, the transfer of nine embryos to four cows produced a transgenic offspring, greatly reducing the time and costs involved (Cibelli, 1998). Using the nuclear transfer approach, an entire herd of transgenic cattle could be produced in one generation at a time savings of about two years for each generation (Cibelli, 1998).

The researchers have not yet created a cow that can produce a drug, but, at the time of their report, there were pregnant cows carrying female fetuses that have been altered to produce milk with the human serum albumin (Weiss, 1998e). Serum albumin is used to treat patients suffering from burns or other injuries that require an increase in blood volume. Advanced Cell Technology, the company founded by the researchers, already has made an arrangement with Genzyme Transgenics Corp. to produce albumin (Weiss, 1998e).

Cloning Transgenic Goats

Scientists have succeeded in cloning three identical female transgenic goats that secrete human antithrombin III in their milk. The goats, born in October 1998, were produced by nuclear transfer using cells derived from a 40-day old transgenic female fetus that carried the human gene for antithrombin III (Baguisi, et al., 1999). The qualities that make dairy goats ideal for transgenic production of biopharmaceuticals, include their short gestation time relative to cattle and their ability to produce two to three times as much milk as a sheep.

Antithrombin III, which prevents blood from clotting, is usually made from plasma of donated blood. However, since quantities of antithrombin III from plasma are usually small and there is a risk of contamination, scientist have turned to transgenic animals for an alternative source of the protein. Enough antithrombin III was obtained from the three cloned goats to supply three phase-three clinical trials that are testing the protein in patients who are not able to produce enough in their own bodies (BBC, 1999).

Therapeutic Uses of Cloning Technology

Beyond their use in cloning for reproductive purposes, the fundamental techniques of somatic cell nuclear transfer have also been used to develop novel therapeutic applications. For example, nuclear transfer technology has been used for preimplantation diagnosis during IVF, to try to treat infertility, and in an attempt to produce human embryonic stem cells. These accomplishments illustrate the potential of somatic cell nuclear transfer technology for therapeutic purposes.

Cloning Technology Used in Preimplantation Diagnosis

In order to test IVF embryos for genetic and chromosomal abnormalities before the embryo is implanted into a woman's uterus, a few cells can be taken from the embryo so that the chromosomes can be examined (karyotyped). However, karyotyping requires that the cells be grown in culture for many hours, days, or even weeks, which greatly reduces the probability of successfully achieving a pregnancy.

To allow more rapid karyotyping of preimplantation embryos, IVF specialists at Saint Barnabas Medical Center in Livingston, New Jersey have developed a technique that uses nuclear transfer technology (Cohen, 1998). By fusing a cell taken from an IVF-created eight-cell human embryo with a very immature cow egg, the chromosomes of the embryonic cell condense and can quickly be karyotyped. The fusion between human cell and cow egg is not viable (Cohen, 1998). The technique was used to screen an embryo made via IVF from a woman who carried a known chromosome defect. Within ten hours, it was established that the embryo did not carry the defect. The embryo was implanted and the woman gave birth to a healthy child (Cohen, 1998).

Although details of the technique have not been published, they were presented at the 1997 meeting of the American Society for Reproductive Medicine.

Nuclear Transfer to Treat Infertility

On October 8, 1998 at the meeting of the American Society for Reproductive Medicine, it was announced that nuclear transfer had been used to treat infertility (Weiss, 1998f). In cases of female infertility where the woman does produce eggs, the problem may be that the eggs are defective. The defect is usually not in the nuclear DNA, but with the cytoplasmic elements that surround the nucleus. Therefore, if the defective cytoplasm could be replaced with "healthy" cytoplasm, an infertile woman might be able to have a genetically related offspring. The researchers removed the nucleus containing the genomic DNA from the infertile women's egg and injected it into a healthy donor's egg whose nucleus had already been removed. When the reconstructed egg was fertilized with sperm in the laboratory, it grew into an embryo that was then implanted in the infertile woman's uterus. At the time of the American Society for Reproductive Medicine meeting, it was not known whether this technique had resulted in a live birth. This technique does not constitute cloning, since any resulting child would have genes from a father as well as a mother. However, it is similar enough to cloning that it would be illegal in California and possibly some other states that have broadly worded anti-cloning legislation (Weiss, 1998f).

An earlier report, published in the July 19, 1997 issue of *The Lancet*, describes a related technique to treat infertility caused by cytoplasmic deficiencies (Cohen, et al., 1997). Scientists from Saint Barnabas Medical Center's Institute for Reproductive Medicine and Science in Livingston, New Jersey and Tel Hashomer Hospital in Tel-Aviv, Israel were able to treat a woman with cytoplasmic deficiencies by performing cytoplasm transfer with ooplasm from donor eggs transferred into the patient's eggs (Cohen, et al., 1997). The husband's sperm along with the donor ooplasm were simultaneously inserted into the patient's eggs (Cohen, et al., 1997). Four developing embryos were transferred to the patient's uterus, resulting in a singleton pregnancy and a baby girl born at term (Cohen, et al., 1997).

Adult Human Cheek Cell Fused with Enucleated Cow Oocyte

Advanced Cell Technology of Worcester, Mass. announced Wednesday, November 11, 1998, that its scientists had for the first time made human cells revert to the primordial, embryonic state from which all other cells develop, by fusing them with cow eggs and creating a hybrid cell (Wade, 1998). This work with human cells was performed in 1996 by Jose Cibelli. Using 52 of his own cells, some of them white blood cells and others scraped from the inside of his cheek, Cibelli used a pulse of electricity to fuse each cell with a cow egg from which the nucleus containing the DNA had first been removed (PCT/U397/12919, 1997). Out of these 52 attempts, only one embryo, derived from a cheek epithelial cell, developed into a blastocyst. Approximately 12 days after the fusion of cheek cell and cow egg, there were sufficient cells to allow harvesting of the inner cell mass to produce cells resembling embryonic stem cells

(PCT/U397/12919, 1997). The scientists observed that the hybrid cell quickly became more human-like as the human nucleus took control and displaced cow proteins with human proteins. However, it is difficult to judge the validity of this work since it is extremely preliminary and has not been submitted for peer review or publication in a scientific journal.

The researchers emphasized that they had no intention of transferring the resulting hybrid embryos to a uterus, something they considered to be unethical and unsafe (Wade, 1998). The stated purpose of these experiments was to create an embryo solely for the purpose of establishing an embryonic stem cell line that could potentially be used to treat any disease caused by loss or malfunction of cells, such as Parkinson's disease, diabetes, and heart disease. However, it is unclear whether this technique will be a feasible technique for creating embryonic stem cells for transplantation purposes. If mitochondria from the cow egg remain, there may be problems with these cow-human hybrids. The mitochondrial genes that are left behind in the cytoplasm of the cow eggs may clash with genetic information contained in the nucleus from the human donor cell and make it impossible to use the resulting cells for transplantation. If it is possible to remove the cow mitochondria and replace them with human mitochondria, it may be possible to overcome these problems.

Cloning – Potential Risks

Since the cloning of Dolly, advances in the field of somatic cell nuclear transfer cloning have occurred very quickly. However, the application of this technology to the cloning of mammals is still new, and the potential problems that may arise are not well understood. It has been quite clear from the start that somatic cell nuclear transfer cloning is associated with high rates of failure contributed to by high rates of spontaneous abortion late in pregnancy and death soon after birth, but it will take time before other risks are discovered. A couple of recent reports provide additional evidence that somatic cell nuclear transfer is not without its problems. These potential dangers highlight one of the core arguments against the use of somatic cloning for reproductive purposes in human beings, that of safety.

Cloning Linked to Developmental Defects of the Immune System

In May 1999, researchers in France reported that a calf, cloned from the ear of a 15-day old calf, died after 51 days from severe anemia (Renard et al., 1999). An autopsy revealed atrophy of the thymus, under-development of the thymus, spleen, and lymph nodes, and no development of lymphocytes (Renard et al., 1999). No other evidence of infection, malformation, or other abnormalities were found (Renard et al., 1999). It is thought that these abnormalities were probably caused by either a random mutation in the donor cell that was used, or a problem with the reprogramming of the somatic cell that occurred during the cloning process (Renard et al., 1999). These abnormalities of the immune system are the first reported developmental defects linked to cloning by somatic cell nuclear transfer, and bring to the forefront the question of safety.

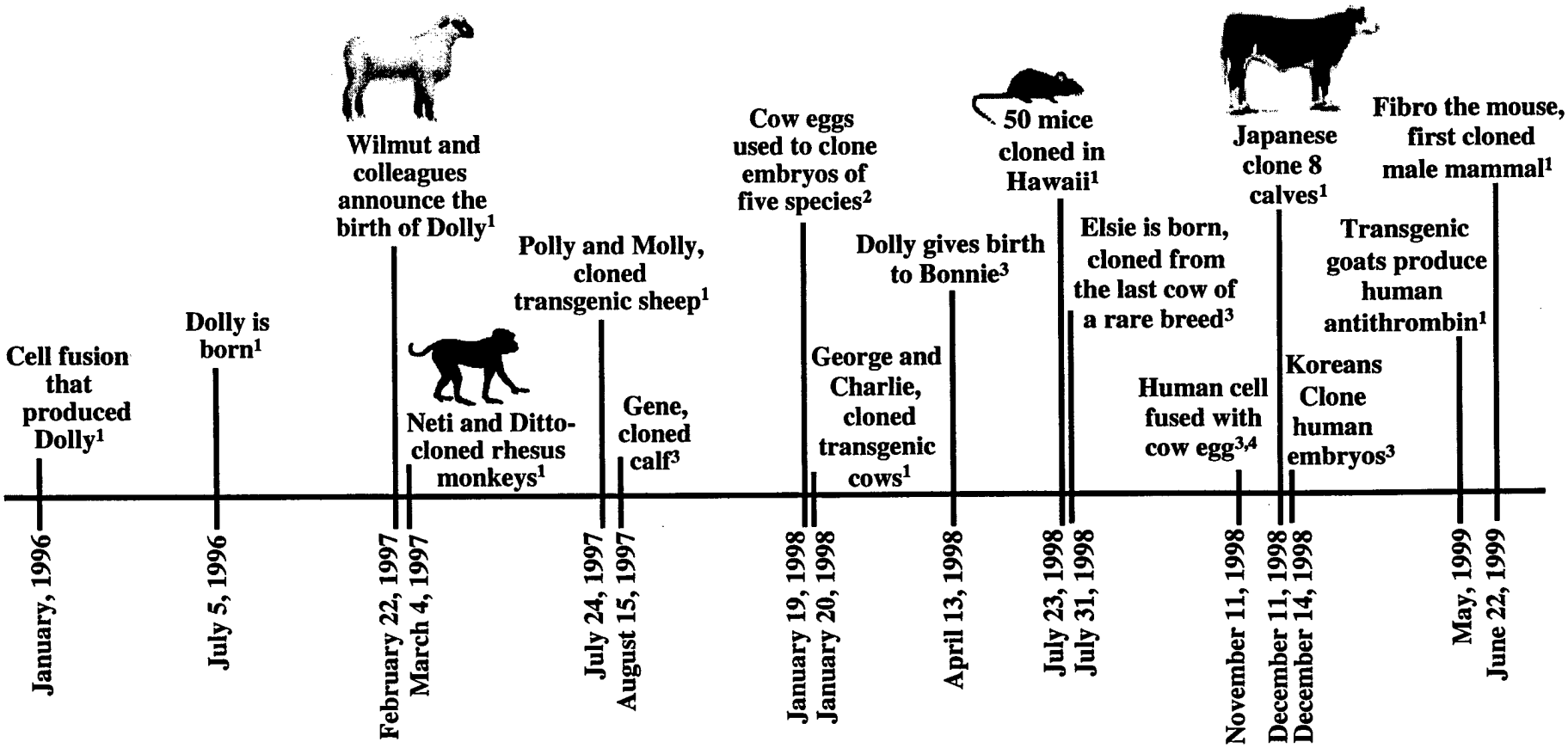
Dolly's Cells Appear to be Older than She Is

When it was announced that Dolly was cloned using a cell from a six year old sheep, several questions were asked about her age. How old is Dolly? Did the clock start over when she was born, or did it keep ticking? Should six years be added to her age to account for the age of the donor cell from which she was cloned? A recent report in the journal *Nature* concludes that Dolly's cells appear to be older than she is.

A team of scientists, including those that cloned Dolly, have measured the telomeres in her cells as an indication of her actual age (Shiels et al., 1999). Telomeres are repeated sequences of DNA at the end of chromosomes that get progressively shorter every time a cell divides. Over time, as an animal ages or as cells divide in the laboratory, the telomeres get shorter. The length of Dolly's telomeres was compared to telomere length in other sheep her age, and it was found that Dolly's telomeres were approximately 20 percent shorter (Shiels et al., 1999). Telomeres from a sheep cloned from embryonic cells and a sheep cloned from fetal cells were also examined and found to be shorter than other sheep matched for age that were not cloned (Shiels et al., 1999). However, it is not known if the shorter telomeres actually make a difference in the physiological age of the cloned sheep, and whether or not the cloned sheep will die earlier due to premature aging of their cells (Shiels et al., 1999).

Other scientists, however, are not convinced that the findings of shorter telomeres in the cloned sheep are meaningful. They question whether the 20 percent difference detected is truly significant or is just within the normal variation for sheep, and if the techniques used are even sensitive enough to detect the differences reported (Kolata, 1999). The significance of these results will not be clear until this type of experiment is performed on other cloned animals.

Figure 1. Timeline of Scientific Developments in Cloning



[1]Published in a peer reviewed journal.
[2]Reported at a scientific meeting.
[3]Reported in the popular press.
[4]This work was originally performed in 1996, but not report until over 2 years later.

LEGISLATIVE UPDATE

Almost immediately after the announcement of Dolly's birth, legislation was introduced in the 105th Congress and approximately a dozen states, aimed at prohibiting the cloning of human beings (NBAC, 1997). President Clinton also transmitted legislation to Congress that would make it illegal for anyone to create a human being through cloning. More recently, two bills have been introduced in the 106th Congress. While there was no law in the United States that directly prohibited creating a child through somatic cell nuclear transfer, there were already a variety of state and federal laws and some existing policies that did apply. Outlined below are enacted and pending legislation at the federal and state levels that both directly and indirectly prohibit the cloning of human beings (Tables 1-6).

Administration Policy

On March 4, 1997, President Clinton released a statement to the heads of executive departments and agencies prohibiting the use of federal funds for cloning of human beings. Even though restrictions already exist on the use of federal funds for the creation of human embryos for research purposes (see Federal Legislation below), these restrictions do not explicitly cover the creation of human embryos for implantation and do not cover all federal agencies. Therefore, President Clinton issued his statement "to make it absolutely clear that no federal funds shall be allocated for cloning of human beings."

Acting on NBAC's key recommendation, President Clinton announced the "Cloning Prohibition Act" of 1997 on June 9, 1997. Consistent with the NBAC's recommendation, the President's legislative proposal prohibited the use of somatic cell nuclear transfer to create a human being for five years and directed the NBAC to report to the President in four and a half years on whether to continue the ban. The proposal was carefully worded to ensure that it would not interfere with beneficial biomedical and agricultural activities. This legislation, therefore, would not prohibit the use of somatic cell nuclear transfer techniques to clone DNA in cells and it would not ban the cloning of animals. To date, this legislation has not been signed into law, however, the ban on federal funding the President declared in March remains in effect. In addition, the President called upon the private sector to refrain voluntarily from using this technology to attempt to clone a human being.

A Statement of Administrative Policy was released by the Office of Management and Budget on February 9, 1998, in response to Senator Lott's Human Cloning Prohibition Act (S.1601, see below). The Statement detailed the Administration's position that it did not support the passage of S.1601 in its current form because it was "too far-reaching" and it would "prohibit important biomedical research aimed at preventing and treating serious and life-threatening diseases." Instead, the Administration offered several amendments to S.1601, including: 1) a five year sunset on the prohibition on human somatic cell nuclear transfer technology to ensure that there is a continuing examination of the risks and benefits; 2) permitting somatic cell nuclear

transfer using human cells for the purpose of developing stem cell technology; 3) striking the bill's criminal penalties and instead making any property derived from or used to commit violations of the Act subject to forfeiture to the United States; and 4) striking the provision establishing a new Commission to Promote a National Dialogue on Bioethics, since it would be duplicative of NBAC's mission. The President's proposal would "prohibit any attempt to create a human being using somatic cell nuclear transfer, provide for further review of the ethical and scientific issues associated with the use of somatic cell nuclear transfer, and protect important biomedical research."

Federal Legislation

In fiscal years 1996 and 1997, Congress passed prohibitions on the use of funds appropriated to the Departments of Labor, Health and Human Services, and Education, and Related Agencies for any research that involves exposing embryos to risk of destruction for non-therapeutic research (P.L. 104-91 and P.L. 104-208). The net effect of these appropriation decisions has been to eliminate virtually all federal funding for research to perfect methods for cloning human beings, including research aimed at initiating pregnancy, since it would probably involve the destruction of many embryos that failed to develop normally (NBAC, 1997). This type of research could, however proceed uninhibited in the private sector.

More recently, language that directly prohibits the use of federal funds for cloning of humans beings has been included in the appropriations legislation for the Departments of Labor, Health and Human Services, and Education, and Related Agencies in fiscal years 1998 and 1999 (Table 1). These appropriations continue the human embryo research ban in the public sector by prohibiting the use of federal funds for the creation of a human embryo for research purposes or for research in which a human embryo is destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero. By expanding the definition of a human embryo to "include any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells" (P.L. 105-78 and P.L. 105-277), these appropriations also effectively prohibit the use of federal funds for the cloning of human beings.

There are two other federal laws and policies that do not directly prohibit cloning, but may have some applicability. The *Fertility Clinic Success Rate and Certification Act of 1992* (42 U.S.C.A. Sec, 263a-1 et seq) requires that clinics using assisted reproduction techniques, such as in vitro fertilization, be monitored. The Act covers all laboratories and treatments that involve manipulation of human eggs and embryos, and requires that pregnancy success rates be reported to the Department of Health and Human Services (DHHS) for publication in a consumer guide. DHHS is also directed to develop a model program to be implemented by the states for the inspection and certification of laboratories that use human embryos. Since any effort to use cloning to create a child would involve manipulation of human eggs and embryos, these requirements would probably also apply to efforts to clone human beings.

The *Federal Policy for the Protection of Human Subjects* (also called the "*Common Rule*") describes the requirements for conducting research on human subjects, such as ensuring that human subjects are not exposed to unreasonably risky experiments and are enrolled in research only after giving informed consent (45 C.F.R. Part 46, Subpart A). The *Common Rule*, promulgated by 17 federal agencies that conduct, support or otherwise regulate human subjects research, governs research that is conducted with federal funds or is performed at institutions that have executed an assurance with the Federal Government.[2] Other human subjects regulations codified at Title 45 Part 46 of the Code of Federal Regulations include additional protections pertaining to research involving fetuses, pregnant women and human IVF. Enforcement of these protections is primarily the responsibility of Institutional Review Boards (IRBs), which review experiments before people can be enrolled. Any effort to use federal funds to clone a human being would raise serious questions about the physical harms that might result, making it difficult for an IRB to approve such research.

To date, two bills prohibiting federal funding of human cloning have been introduced during the 106th Congress (Table 2). H.R.571, sponsored by Representative Paul, prohibits "federal payments to any business, institution, or organization that engages in human cloning or human cloning techniques." H.R.2326, sponsored by Representative Stearns, prohibits the use of Federal funds to "conduct or support any project of research that includes the use of somatic cell nuclear transfer technology to produce an oocyte that is undergoing cell division toward development of a fetus." H.R.2326 is identical to Representative Stearns' cloning bill from the 105th Congress.

In the 105th Congress, nine bills were introduced dealing directly with the cloning of a human beings, six in the Senate and three in the House (Table 3). These bills have several similarities as well as some differences. While no action was taken on any of these bills before the 105th Congress adjourned, one bill, H.R. 3133, has already been reintroduced in the 106th Congress (see above). Therefore, a summary of the bills introduced in the 105th Congress is also provided

All of the bills make it unlawful to clone a human being or to conduct research for the purpose of cloning a human being. Some bills specifically prohibit the use of somatic cell nuclear transfer to clone a human being (S.1602, S.1611, S.1601, S.1599, H.R. 923), while others are more general (H.R.571, S.1574, S.368, H.R.922, H.R. 3133). Some of the bills expressly prohibit the use of federal funds for research regarding the cloning of a human being (H.R.571, S.1574, S.368, H.R. 922, H.R.3133). Some of the bills also set forth specific penalties for these actions including fines, prison time, and the forfeiture of property (S.1574, S.1602, S.1611, H.R. 923. S.1601, S.1599). Furthermore, a few bills contain language about international cooperation to

[2] These assurances typically promise that any researcher affiliated with the institution will abide by the Federal regulations even if that particular researcher is not using Federal funds.

enforce mutually supported restrictions on the prohibition of the cloning of human beings (S.1602, 1611, H.R.3133, S.1601, S.1599).

A few of the bills also contain language that strives not to restrict areas of biomedical and agricultural research such as research or practices involving the use of: (1) somatic cell nuclear transfer or other cloning technologies to clone molecules, DNA, cells, and tissues; (2) mitochondrial, cytoplasmic or gene therapy; or (3) somatic cell nuclear transfer techniques to create nonhuman animals (S.1602, S.1611, H.R.922, H.R.3133). Two bills even provide for the preemption of any state or local law that prohibits or restricts research regarding somatic cell nuclear transfer, mitochondrial or cytoplasmic therapy, or the cloning of molecules, DNA, cells, tissues, organs, plants, animals, or humans (S.1602, S.1611).

At least four bills provide for further review of the ethical and scientific issues associated with the use of somatic cell nuclear transfer in human beings, and the impact of its prohibition. One bill designates the National Bioethics Advisory Commission to submit a report to the President and the Congress concerning these matters and authorizes the continuation of the Commission for a ten-year period (S.1602). Another bill, establishes a new group within the Institute of Medicine called the National Commission to Promote a National Dialogue on Bioethics to provide an independent forum for broad public participation and discourse concerning important bioethical issues, including cloning (S.1601, S.1599). Finally, two bills require the Director of the National Science Foundation to enter into an agreement with the National Research Council to review the implementation of any legislation prohibiting the cloning of human beings (H.R.922, H.R.3133).

Table 1. Enacted Federal Legislation Prohibiting Cloning of Human Beings

PUBLIC LAW #	TITLE	SYNOPSIS	STATUS
P.L. 105-277	Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1999 (part of the Omnibus Appropriations Bill FY99)	Continues the ban on the use of Federal research funds for human embryo research. This means that Federal funds may not be used for the creation of a human embryo for research purposes or for research in which a human embryo is destroyed, discarded or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero. The definition of a human embryo includes "any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells."	Sponsor: Rep Wolf Introduced as H.R. 4328: 07/20/98 Became Public Law 105-277: 10/21/98
P.L. 105-78	Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1998	Continues the ban on the use of Federal research funds for human embryo research. This means that Federal funds may not be used for the creation of a human embryo for research purposes or for research in which a human embryo is destroyed, discarded or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero. Congress also expanded the definition of a human embryo to "include any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells."	Sponsor: Rep. Porter Introduced as H.R. 2264: 07/25/97 Became Public Law: 105-78: 11/13/97

Table 2. Pending Federal Cloning Legislation in the 106th Congress

BILL #	TITLE	SYNOPSIS	STATUS
H.R.571.IH	Human Cloning Prevention Act of 1999	Prohibits Federal payments to any business, institution, or organization that engages in human cloning or human cloning techniques.	Sponsor: Rep. Paul Introduced in the House: 02/04/99
H.R.2326.IH	Human Cloning Research Prohibition Act	Prohibits the expenditure of the Federal funds to conduct or support research on the cloning of humans, and to express the sense of the Congress that other countries should establish substantially equivalent restrictions.	Sponsor: Rep. Stearns Introduced in the House: 06/23/99

Table 3. Proposed Federal Cloning Legislation in the 105th Congress

BILL #	TITLE	SYNOPSIS	STATUS
S.368.IS	To prohibit the use of Federal funds for human cloning research	Prohibits the use of Federal funds for research regarding the cloning of a human individual.	Sponsor: Senator Bond Introduced in the Senate: 02/27/98
S.1611.PCS	Prohibition on Cloning of Human Beings Act of 1998	see S.1602.IS	Sponsor: Senator Feinstein Placed in the Senate: 02/04/98
S.1602.IS	Prohibition on Cloning of Human Beings Act of 1998	Amends the Public Health Service Act to make it unlawful for any person or other legal entity to (1) implant or attempt to implant the product of somatic cell nuclear transfer into a woman's uterus; (2) ship the product of somatic cell nuclear transfer in interstate or foreign commerce for the purpose of implanting such product into a woman's uterus, in the United States or elsewhere; or (3) use funds made available under this Act, or any other Act, for an activity prohibited by this Act. Requires the National Bioethics Advisory Commission to submit a report to the President and the Congress concerning current information on cloning. Authorizes the continuation of the Commission for a ten-year period. Sets forth, with respect to violations of the cloning prohibition, requirements for: (1) civil penalties; (2) civil actions; and (3) the forfeiture of certain property.	Sponsor: Senator Feinstein Introduced in the Senate: 02/03/98
S.1601.PCS	Cloning Prohibition Act	Amends the Federal criminal code to prohibit any person or entity: (1) in or affecting interstate commerce, from using human somatic cell nuclear transfer technology; and (2) from importing an embryo produced through such technology. Sets penalties for violations of this Act of: (1) up to ten years in prison, a fine, or both; and (2) not more than twice the amount of any gross pecuniary gain derived from such violation. Establishes within the Institute of Medicine the National Commission to Promote a National Dialogue on Bioethics.	Sponsor: Senator Lott Placed in the Senate: 02/03/98

Table 3. Proposed Federal Cloning Legislation in the 105th Congress (continued)

S.1574.IS	Human Cloning Prohibition Act	Makes it unlawful for any person to: (1) clone a human being; or (2) conduct research for the purpose of cloning a human being or otherwise creating a human embryo. Prohibits Federal funds from being obligated or expended to knowingly conduct any research project to clone a human being or otherwise create a human embryo. Sets forth a civil money penalty. Prohibits an individual found to be in violation of the prohibition from receiving any Federal funding for research for a period of five years after such violation.	Sponsor: Senator Campbell Introduced in the Senate: 02/03/98
S.1599.IS	Cloning Prohibition Act of 1998	see S.1601.PCS	Sponsor: Senator Bond Introduced in the Senate: 02/03/98
H.R.3133.IH	Cloning Research Prohibition Act	Prohibits the expenditure of Federal funds to conduct or support research on the cloning of humans, and expresses the sense of the Congress that other countries should establish substantially equivalent restrictions.	Sponsor: Rep. Stearns Introduced in the House: 01/28/98
H.R.923.IH	Human Cloning Prohibition Act	Makes it unlawful for any person to use a human somatic cell for the process of producing a human clone. Sets forth a civil money penalty.	Sponsor: Rep. Ehlers Introduced in the House: 03/05/97
H.R.922.IH	Cloning Research Prohibition Act	Prohibits the expenditure of Federal funds to conduct or support any research on the cloning of humans. Directs the Director of the National Science Foundation to enter into an agreement with the National Research Council for a review of the implementation of this Act.	Sponsor: Rep. Ehlers Introduced in the House: 03/05/97

State Legislation

Even though most states do not have legislation directly regulating assisted reproduction techniques, a number of state laws regarding the management of embryos could restrict even privately funded research aimed at cloning human beings (NBAC, 1997). Ten states have laws regulating research and/or experimentation on conceptuses, embryos, fetuses or unborn children that use broad enough language to include early stage conceptuses: Florida, Louisiana, Maine, Massachusetts, Michigan, Minnesota, North Dakota, New Hampshire, Pennsylvania, and Rhode Island (NBAC, 1997).

Five states have enacted legislation that directly prohibits cloning of a human being, California, Louisiana, Missouri, Michigan and Rhode Island (Table 4). California was the first state to enact legislation prohibiting the cloning of human beings. Within three weeks of the announcement of the cloning of Dolly, California introduced a bill into the Senate (SB1344). The bill was signed into law by the Governor on October 4, 1997.

Michigan has enacted four separate bills all prohibiting cloning of human beings. Three bills were introduced in the House (HB5475, HB4846, and HB4962), and one bill was introduced in the Senate (SB864). All three of the House bills needed to be enacted into law for each act to take effect. All four bills passed the Senate by a vote of 37 to zero. In addition, all four bills were presented to Governor for signature on May 20, 1998, and signed into law by the Governor on June 3, 1998.

Rhode Island and Missouri both introduced bills in January 1998. In Rhode Island, the bill became law without the Governor's signature on July 7, 1998 (HB7123). In Missouri, the bill was signed into law by the Governor on July 10, 1998 (SB722). Louisiana is the latest state to enacted cloning legislation. Legislation banning the cloning of human beings was introduced into Louisiana's Senate on March 29, 1999, and signed into law by the Governor on July 2, 1999 (SB825).

In addition, there are four states that have pending legislation to prohibit the cloning of human beings (Table 5). Massachusetts has three bills pending, New York has five bills pending, and New Jersey and Ohio each have one bill pending. Six states, Arkansas, Connecticut, Illinois, Oregon, South Carolina and Virginia, introduced proposed legislation, however bills in these states are now inactive because of the adjournment of their legislatures (Table 6).

Table 4. Enacted State Cloning Legislation[3]

STATE	BILL #	SYNOPSIS	STATUS
California	SB1344	Prohibits a person from cloning a human being and from purchasing or selling ovum, zygote, embryo, or fetus for cloning purposes. Penalties for a corporation not to exceed $1,000,000, penalties for an individual $250,000. Those in violation may lose their license. Provisions will be repealed on 1/1/03 unless a later enacted statue deletes or extends that date.	Sponsor: Johnston Introduced: 3/11/97. Amended in Senate: 4/21/97. Amended in Assembly: 8/25/97. Passed Assembly: 9/2/97. Passed Senate: 9/10/97. Signed by the Governor: 10/4/97. Filed with Secretary of State: 10/6/97.
Louisiana	SB825	Prohibits human cloning.	Sponsor: Hines Introduced: 3/29/99. Referred to Senate Cmmt. on Health and Welfare: 3/29/99. Reported with amendment from Senate Cmmt. on Health and Welfare: 5/5/99. Cmmt. amendment adopted by Senate: 5/6/99. Passed Senate: 5/11/99. Sent to House Cmmt. on Health and Welfare: 5/12/99. Reported favorably from House Cmmt. on Health and Welfare; referred to Legislative Bureau: 5/27/99. Reported from Legislative Bureau with amendments, and amendments adopted: 6/1/99. Passed House; to Senate for concurrence: 6/14/99. Senate concurred in House amendments: 6/17/99. Signed by Governor: 7/2/99.
Michigan	HB4846	Amends the Public Health Code relating to the practice of a health profession by a licensee, a registrant, or an applicant for licensure or regulation. Prohibits a licensee or registrant or other individual from cloning or attempting to clone a human being. A licensee or registrant or other individual who violates this subsection is subject to a civil penalty of $10,000,000.	Sponsor: Profit Introduced: 1/14/98. Passed House: 1/29/98. Passed Senate by a 37-0 vote: 4/28/98. Bill received House concurrence and with SB864, HB5475, HB4962 was presented to Governor for signature: 5/20/98. Signed by the Governor: 6/3/98.

[3] From Pharmaceutical Research and Manufacturers of America (PHRMA), Cloning Legislation and Regulation, http://www.phrma.org/genomics/cloning/legislation.html

Table 4. Enacted State Cloning Legislation (continued)

STATE	BILL #	SYNOPSIS	STATUS
Michigan	HB4962	Amends the Penal Code to prohibit an individual from cloning or attempting to clone a human being. Provides felony penalties of not more than 10 years imprisonment or a fine of not more than $5,000.00 or both. Definitions of "clone", "cloning", "human somatic cell nuclear transfer" and "somatic cell" are the same as in HB 4846.	Sponsor: McManus Introduced: 1/14/98. Passed House: 1/29/98. Passed Senate by a 37-0 vote: 4/28/98. Bill received House concurrence and with SB864, HB5475, HB4846 was presented to Governor for signature: 5/20/98. Signed by the Governor: 6/3/98.
Michigan	HB5475	Prohibits the expenditure of state funds to clone a human being or to conduct or to support research on the cloning of human beings. Definitions are the same as HB 4846 and HB 4962. All three bills must be enacted into law for each act to take effect.	Sponsor: Mans Introduced: 1/14/98. Passed the House: 1/29/98. Passed Senate by a 37-0 vote: 4/28/98. Bill received House concurrence and with SB 864, HB4962, HB4846 was presented to Governor for signature: 5/20/98. Signed by the Governor: 6/3/98.
Michigan	SB864	Prohibits human cloning for a period of 5 years and provides for civil and criminal penalties.	Sponsor: Bennett Introduced: 2/5/98. Passed Senate by a 37-0 vote: 4/28/98. SB864, HB4846, HB 4962 & HB 5475 were concurred and presented to Governor for signature: 5/22/98. Signed by the Governor: 6/3/98.
Missouri	SB722	The Senate bill incorporates HB 1316. Section 17 of the bill states that no state funds shall be used for research with respect to the cloning of a human person. For purposes of this section, the term "cloning" means the replication of a human person by taking a cell with genetic material and cultivating such cell through the egg, embryo, fetal and newborn stages of development into a new human person.	Sponsor: Sims Introduced: 1/14/98. Cmmt. substitute adopted on Senate floor and passed Senate: 3/4/98. House Cmmt. on Insurance passed as substituted: 4/21/98. Amended on House Floor: 5/5/98 & 5/6/98. Passed House; to the Senate for concurrence: 5/6/98. Senate concurred in House amendments: 5/8/98. Signed by the Governor: 7/10/98.
Rhode Island	HB7123	Prohibits cloning of a human being and purchasing or selling of an ovum, zygote, embryo, or fetus for the purpose of cloning a human being. Provides for civil penalties in the amount not to exceed $1,000,000 for a corporation, etc.; not to exceed $250,000 for an individual for violations of the act.	Sponsor: Cambio Introduced: 1/9/98. Amended on the House floor and passed House: 4/29/98. Passed on Senate Floor: 6/26/98. House concurred with amendment: 6/29/98 Became law without Governor's signature: 7/7/98.

Table 5. Pending State Legislation[4]

STATE	BILL #	SYNOPSIS	STATUS
Massachusetts	HB2455	Prohibits science of cloning.	Sponsor: Fallon Introduced 1/6/99.
Massachusetts	HB2462	Regulates the science of cloning.	Sponsor: Harkins Introduced 1/6/99.
Massachusetts	SB1394	Prohibits human cloning.	Sponsor: Magnani Introduced: 1/6/99. Referred to Senate Cmmt. on Science and Technology: 1/6/99.
New Jersey	AB329	States that a person who knowingly engages or assists, directly or indirectly, in the cloning of a human being is guilty of a crime of the first degree. Defines "cloning of a human being" to mean the replication of a human individual by cultivating a cell with genetic material through the egg, embryo, fetal and newborn stages into a new human individual. Amends the Genetic Privacy Act of 1996 to provide that an individual's genetic information is the property of the individual, and deletes exceptions from current New Jersey law where procedures for obtaining informed written consent already are governed by national standards.	Sponsors: Doria and Gill Introduced: 1/13/98 Referred to Assembly Health Cmmt.: 1/13/98 Carryover to 1999 legislative session.
New York	SB2123	Provides that appropriations and reappropriations to the New York State Advisory Commission on Cloning and Genetic Engineering shall be subject to the provisions which apply to all other legislative commissions; creates the temporary state commission on cloning and genetic engineering to examine, evaluate and make recommendations to the Legislature and Governor on the scientific, technical, moral and ethical issues raised by cloning.	Sponsor: Goodman Introduced: 2/3/99. Referred to Senate Cmmt. on Finance: 2/3/99. Withdrawn from Senate Cmmt. on Finance: 3/18/99. Referred to Senate Cmmt. on Corporations, Authorities, and Commissions: 3/18/99.
New York	SB1954	Enacts Cloning Prohibition and Research Protection Act, prohibits cloning of human beings and provides a $250 civil fine for violation of prohibition.	Sponsor: Goodman Introduced: 2/1/99. Referred to Senate Cmmt. on Health: 2/1/99.

[4] From Pharmaceutical Research and Manufacturers of America (PHRMA), Cloning Legislation and Regulation, http://www.phrma.org/genomics/cloning/legislation.html

Table 5. Pending State Legislation (continued)

STATE	BILL #	SYNOPSIS	STATUS
New York	SB1179	Prohibits any person from cloning a human and from purchasing or selling an ovum, zygote, embryo, or fetus for the purpose of cloning a human and establishes civil penalties of up to a specified amount.	Sponsor: Marchi Introduced: 1/15/99. Referred to Senate Cmmt. on Health: 1/15/99.
New York	AB6874	Prohibits human cloning and the use of public funds, resources, property, employees, or those of political subdivisions or public corporations in furtherance thereof; makes violation a felony and grounds for license revocation.	Sponsor: Labriola Introduced: 3/10/99. Referred to Assembly Cmmt. on Health: 3/10/99.
New York	AB3026	Prohibits any person from cloning a human being and from purchasing or selling an ovum, zygote, embryo, or fetus for the purpose of cloning a human being; establishes civil penalties; requires the Commissioner of Health to submit a report to the Governor and the Legislature on the implications of human cloning.	Sponsor: Connelly Introduced: 1/28/99. Referred to Assembly Cmmt. on Health: 1/28/99.
Ohio	SB102	Prohibits cloning a human being. Makes it unlawful to purchase or sell an ovum, zygote, embryo, or fetus for the purpose of cloning. Creates a "Cloning Enforcement Fund" in the state treasury which would consist of moneys from civil penalties. Civil penalty would not exceed $5,000.	Sponsor: Ray Introduced: 3/11/99. Referred to Senate Cmmt. on Reference: 3/11/99. Senate Cmmt. on Reference recommended referral: 3/16/99. Sent to Senate for second reading; read a second time: 3/16/99. Sent to Senate Cmmt. on Judiciary: 3/16/99. Hearing in Senate Cmmt. on Judiciary: 4/21/99

Table 6. Inactive State Legislation[5]

STATE	BILL #	SYNOPSIS	STATUS
Arkansas	SB476	An act to prohibit cloning. Would place no restrictions on biomedical research, require no private right of action, and would provide civil penalties.	Sponsor: Edwards Introduced: 2/15/99. Referred to Senate Cmmt. on Public Health, Welfare, and Labor: 2/15/99. Passed the Senate; to House: 2/22/99. Referred to House Cmmt. on Public Health and Welfare: 2/23/99. Passed as amended by Cmmt. on Public Health, Welfare and Labor: 3/16/99. Cmmt. amendment adopted on House Floor: 3/31/99. Failed to pass House: 4/8/99. Arkansas legislature adjourned: 4/9/99.
Connecticut	HB5042	Protects society from potential abuse of cloning technologies by prohibiting the cloning of an entire human being, while not restricting biomedical research for purposes of scientific investigation or cure of diseases or illnesses or the use of medical procedures to assist a woman in becoming pregnant.	Sponsor: Tulisano Prefiled: 12/29/98. Introduced: 1/6/99. Referred to Joint Cmmt. on Judiciary: 1/6/99. Failed Joint Committee favorable deadline: 4/19/99. Connecticut legislature adjourned: 6/9/99.
Illinois	SB649	Prohibits human cloning; establishes administrative penalties for violation; amends the Civil Administrative Code of Illinois, the Ambulatory Surgical Treatment Center Act, the Hospital Licensing Act, and the Medical Practice Act of 1987; provides for revocation of various licenses for violation of the Human Cloning Act; prohibits a person from engaging in activity that involves the use of a human somatic cell for the process of producing a human clone. Provides civil penalties.	Sponsor: Burzynski Introduced: 2/24/99. Referred to Senate Cmmt. on Rules and Executive: 2/24/99. From Senate Cmmt. on Rules and Executive; to subcommittee: 3/4/99. Referred to Senate Cmmt. on Rules: 3/20/99. To Senate Committee on Executive: 5/26/99. Illinois legislature adjourned: 5/27/99.
Oregon	SB794	Creates moratorium on engaging in human cloning.	Sponsor: Lim Introduced: 3/15/99. Referred to Senate Committee on Judiciary: 3/16/99. Oregon legislature adjourned: 7/24/99.

[5] From Pharmaceutical Research and Manufacturers of America (PHRMA), Cloning Legislation and Regulation, http://www.phrma.org/genomics/cloning/legislation.html

Table 6. Inactive State Legislation (continued)

STATE	BILL #	SYNOPSIS	STATUS
South Carolina	HB3036	Makes it unlawful for any person through cloning to grow or create a human being or to conspire to do so, defines cloning for this purpose and provides both civil and criminal penalties for violation.	Sponsor: Mason Introduced 1/12/99 Referred to House Judiciary Committee: 1/12/99. South Carolina legislature adjourned: 6/22/99.
Virginia	HB2418	Prohibits use of cloning techniques to reproduce humans. Bill provides exceptions for biomedical research and gene therapy which do not create human animals. Civil penalties for violation not to exceed $50,000.	Sponsor: Grayson Introduced 1/21/99 Referred to House Committee on Health, Welfare and Institutions: 1/21/99. Virginia legislature adjourned: 2/26/99.
Virginia	HB752	Prohibits human cloning; establishes civil penalties for violation of up to $50,000.	Sponsor: Stump Introduced: 1/23/98 Regular session adjourned: 4/23/98. Carryover to 1999 regular session, commenced: 1/13/99. Virginia legislature adjourned: 2/26/99

REGULATORY UPDATE

Food and Drug Administration

In response to provocative statements by scientist Richard Seed, who announced January 7, 1998 that he plans to clone human beings, the Food and Drug Administration (FDA) announced that it has the authority to regulate human cloning. The FDA asserts that human cloning by somatic cell nuclear transfer requires "more than minimal manipulation" of a cell, and therefore requires approval by the FDA under Section 351 of the *Public Health Service Act* (BNA, 1998). In addition, cellular products resulting from "more than minimal manipulation" of cells would require approval for safety and efficacy under provisions in the *Public Health Service Act* that regulate products derived from human materials (BNA, 1998). Acting Commissioner Michael Friedman has affirmed that the FDA will take legal action against anyone who attempts to clone a human being without obtaining prior approval from the FDA (Price, 1998).

In October of 1998, Stuart L. Nightingale, the Associate Commissioner for Health Affairs at the FDA distributed a letter detailing the FDA's position on the use of cloning technology to create a human being. The purpose of this letter was to confirm to institutional review boards (IRBs) that the FDA has jurisdiction over clinical research involving cloning of human beings, and to inform IRBs of the FDA regulatory process that is required before any investigator can proceed with such a clinical investigation. The letter states:

> "Clinical research using cloning technology to create a human being is subject to FDA regulation under the *Public Health Service Act* and the *Federal Food, Drug, and Cosmetic Act*. Under these statutes and FDA's implementing regulations, before such research may begin, the sponsor of the research is required to submit to FDA an Investigational New Drug Application (IND) describing the proposed research plan; to obtain authorization from a properly constituted and functioning IRB; and to obtain a commitment from the investigators to obtain informed consent from all human subjects of the research. Such research may proceed only when an IND is in effect. Since FDA believes that there are major unresolved safety questions pertaining to the use of cloning technology to create a human being, until those questions are appropriately addressed in the IND, FDA would not permit any such investigation to proceed."

However, the FDA has not specified which provision of current law grants it such authority (Price, 1998). There are three possible bases for FDA's assertion of jurisdiction over cloning of human beings: 1) classification as a "drug" under Section 201(g) of the Federal Food, Drug, and Cosmetic Act (FDCA); 2) classification as a "medical device" under Section 201(h) of the FDCA; and 3) classification as a "biological product" under Section 351(a) of the Public Health Service Act (PHSA) (Price, 1998). If human cloning is covered by any of these statutory provisions, the FDA would have authority to require premarket approval and/or licensing based on reasonable clinical assurance of safety and efficacy (Price, 1998). However, the FDA's authority to regulate cloning of human beings has been questioned, and may require a statutory amendment to expand FDA's authority (Price, 1998).

UPDATE ON CLONING LEGISLATION IN OTHER NATIONS

Due to the transnational characteristics of science, there exists a need for international cooperation regarding the conduct of scientific and medical research. Some of this need may be met through legislation adopted on a country-by-country basis, but some international agreement is probably also needed. NBAC recognized the importance of international cooperation in the effort to prohibit the cloning of human beings, and concluded that "[t]he United States Government should cooperate with other nations and international organizations to enforce any common aspects of their respective policies on the cloning of human beings" (NBAC, 1997).

The possibility of cloning human beings has prompted responses from several nations. Several countries already had existing legislation that prohibited the cloning of human beings, including Australia, Austria, Denmark, France, Germany, Norway, Slovakia, Spain, Sweden, Switzerland, and the United Kingdom. Three countries, Israel, Malaysia and Peru, passed cloning legislation in response to the news of Dolly. In addition, Argentina, Belgium, Canada, China, Japan, and South Korea have proposed legislation but have not yet passed laws to prohibit the cloning of human beings. Countries that already have laws or have announced plans to pass laws prohibiting the cloning of human beings are discussed below and in Table 7.

Countries with Existing Cloning Legislation before Dolly was Cloned

Even though the announcement of the first cloning of an adult mammal seemed to take everyone by surprise, several countries already had existing legislation that prohibited the cloning of human beings. South Australia and Spain have had laws prohibiting the cloning of human beings since 1988. In Victoria, Australia and the United Kingdom legislation was drafted and implemented based on reports from their national ethics commissions. In addition, the ethics commissions in Australia, France and United Kingdom provided their respective governments with additional recommendations after the cloning of Dolly was announced. In contrast, Austria, Norway, Slovakia and Sweden have laws that only implicitly prohibit cloning of human beings.

Australia

Three Australian states, Victoria, South Australia, and Western Australia, already have existing legislation preventing reproductive cloning. In addition, in October 1997, the New South Wales Government issued a discussion paper entitled "Review of the Human Tissue Act 1983." In this paper, the Minister for Health of New South Wales announced that the Government had introduced a law to ban human cloning and trans-species fertilization involving human gametes or embryos. This ban was developed in response to community concern.

The Commonwealth Minister for Health and Aged Care requested the Australian Health Ethics Committee (AHEC) of the National Health and Medical Research Council (NHMRC) to advise him on the need for possible legislation regarding cloning of human beings. In their report

of December 18, 1998, entitled "Scientific, Ethical and Regulatory Considerations Relevant to Cloning of Human Beings," the AHEC advised that:

- "A basic distinction should be drawn between the cloning of a *whole* human individual and the copying (also referred to as "cloning") of the component *parts* of a human (such as DNA and cells);
- The cloning of individual human beings is prohibited by State legislation in Victoria, South Australia and Western Australia and is prohibited by NHMRC guidelines; and
- Legislation should be introduced in the remaining States and Territories to regulate human embryo research and to prohibit research on human embryos except as it is permitted in the NHMRC's *Ethical guidelines on assisted reproductive technology*" (AHEC, 1998).

In addition, the NHMRC's *Ethical guidelines on assisted reproductive technology* already prohibits experimentation with the intent to produce two or more genetically identical individuals, including development of human embryonic stem cell lines with the aim of producing clones of individuals. Although infringement of these guidelines is not a legal offense, sanctions usually involve loss of access to NHMRC research funds. These guidelines are regarded as national standards of acceptable practice.

In May 1998, the Australian Academy of Science initiated a project on human cloning to contribute to the public debate in this area. In February 1999, the Academy released its position statement "On Human Cloning" (AAS, 1999). In its statement, the Academy distinguishes between "reproductive cloning" to produce a human fetus and "therapeutic cloning" to produce human stem cells, tissues and organs, and bases its recommendations on this distinction (AAS, 1999). The Academy's first recommendation states "that reproductive cloning to produce human fetuses is unethical and unsafe and should be prohibited" (AAS, 1999). The statement goes on to say that "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" (AAS, 1999). Based on its recommendations, the Academy concludes that the 1996 NHMRC *Ethical guidelines on assisted reproductive technology* and relevant State legislation should be revised to allow research on therapeutic cloning thereby allowing "Australia to participate fully and capture benefits from recent progress in cloning research" (AAS, 1999).

Denmark

Denmark passed *Act No. 503 on a Scientific Ethical Committee System on the Handling of Biomedical Research Projects* in 1992 (HGAC and HFEA, 1998b). The 1992 Act forbids research on cloning and nuclear substitution. Cloning is defined as the production of genetically identical individuals. In 1997, *Act No. 460 on Medically Assisted Procreation in Connection with Medical Treatment, and Research* confirms the Danish Parliament's position of January 25, 1995, that treatment cannot be initiated in areas where a research ban already exists under the 1992 Act (HGAC and HFEA, 1998b).

France

The Federal Bioethics Legislation, passed in 1994, basically bans embryo research, only allowing research on human embryos if it does not harm the integrity of the embryo. In May 1997, France's national bioethics committee recommended that the ban on human embryo research be loosened to allow for the use of excess embryos from in vitro fertilization for the development of embryonic stem cells for fundamental and therapeutic research (Butler, 1997). The bioethics committee qualified its recommendation with multiple safeguards including requiring informed consent from the parents of the embryo, as well as bans on the creation of embryos for research, germline modifications, and cloning of human beings. The bioethics committee recommended that the legislature adopt their recommendations during the scheduled revision of France's bioethics legislation in 1999 (Butler, 1997).

Germany

Germany already has some of the world's most restrictive laws on genetic engineering, applying even to food plants such as tomatoes and soybeans. The *Federal Embryo Protection Act 1990* makes the creation of an embryo genetically identical to another embryo, fetus or any living or dead person an offense punishable by up to five years imprisonment or by a fine (HGAC and HFEA, 1998b). The Act also prohibits alteration of the genetic information of the human germline, and the creation of chimeras and hybrids. In March 1997, the German Parliament passed a resolution calling for a comprehensive international ban on human cloning.

Spain

Spain's law on *Assisted Reproduction Procedures* (Law No. 35/1988), passed in 1988, explicitly prohibits embryo and oocyte cloning with criminal sanctions (HGAC and HFEA, 1998b). It also prohibits the fertilization of a human ovum for any other purpose than human procreation. This legislation is sufficiently broad enough to prohibit both embryo twinning and somatic cell nuclear transfer because it concentrates on the result rather than the technique used (Knoppers, 1997).

Switzerland

Switzerland's *Law on Reproductive Medicine in Humans* of October 18, 1990, prohibits interventions on the genetic material of gametes, live embryos, and fetuses (International Digest of Health Legislation, 1993). It likewise prohibits measures aimed at influencing the sex or inherited characteristics of the unborn child. Live embryos, fetuses, and parts thereof may not be used for research purposes. Furthermore, the following are prohibited: cloning, the creation of chimeras, interspecies hybridization, and extracorporeal procreation. In addition, Switzerland's Federal Constitution is a legally binding document that implicitly prohibits embryo cloning (HGAC and HFEA, 1998b). Finally, in 1996 Switzerland proposed the *Federal Bill on Medically Assisted Procreation* that would explicitly prohibit the artificial creation of genetically identical beings by imposing criminal sanctions (Knoppers, 1997).

United Kingdom

In Britain, the Human Genetics Advisory Commission (HGAC) and the Human Fertilisation and Embryology Authority (HFEA) recommended that somatic cell nuclear transfer to create embryonic stem cells should be allowed, while the ban on using cloning to create babies should be upheld (HGAC and HFEA, 1998b). In their report issued December 1998, entitled "Cloning Issues in Reproduction, Science and Medicine," it was concluded that the *Human Fertilisation and Embryology Act of 1990* has been effective in dealing with new developments relating to human cloning, and should be extended to ban all human reproductive cloning regardless of the technique used.[6] Under the *Human Fertilisation and Embryology Act of 1990*, laboratory research is allowed on human embryos less than 14 days old only if it is used for research into the treatment of infertility and congenital diseases, but research cannot be aimed at developing replacement tissue. The scientists at HGAC and HFEA advised that the Secretary of State for Health should consider specifying in regulations two further purposes for which the HFEA might issue licenses for research, so that potential benefits can clearly be explored: 1) the development of methods of therapy for mitochondrial disease; and 2) the development of therapeutic treatments for diseased or damaged tissues or organs.

Austria, Norway, Slovakia and Sweden

In contrast to the countries described above that have laws explicitly prohibiting cloning of human beings, the laws in Austria, Norway, Slovakia and Sweden are implicit. Austria's Federal Law of 1992 regulating Medically Assisted Procreation implicitly prohibits cloning of human beings by stating that assisted reproductive techniques must use "viable cells" to achieve pregnancy (Knoppers, 1997). Sweden's Law No. 115, passed on March 14, 1991, implicitly prohibits embryo and oocyte cloning with criminal sanctions (HGAC and HFEA, 1998b). Section 2 states that "the purpose of experimentation shall not be to develop methods aimed at causing heritable genetic effects." Norway's *Law No. 56 on the Medical Use of Biotechnology 1994* and Slovakia's 1994 *Health Care Law* also implicitly prohibit embryo cloning (HGAC and HFEA, 1998b).

Countries that Passed Cloning Legislation in Response to the News of Dolly

Three countries, Israel, Malaysia and Peru, passed cloning legislation in response to the news of Dolly. Legislation was passed in both Malaysia and Peru because cloning of human beings was viewed as unnatural. However in Malaysia, cloning of animals for scientific purposes is allowed. In Israel, there is a five year moratorium on cloning of human beings, however the law

---

[6]The 1990 Act expressly prohibits one type of cloning technique, the "nuclear substitution of any cell whilst it forms part of an embryo" (HGAC and HFEA, 1998a, b). However, it does not expressly prohibit embryo splitting or nuclear transplantation. Since both of these techniques involve the creation of embryos outside the body, a license is required. In 1997, the HFEA announced a policy not to issue licenses for any procedures involving embryo splitting or nuclear transfer to any IVF practice either in the private or public sector.

allows cloning for medical purposes if the Health Minister deems that it does not violate human dignity.

Israel

The Israeli Knesset unanimously passed an anti-genetic intervention law on December 29, 1998. The law places a five year moratorium on any attempt to clone human beings. Germ-line gene therapy is also forbidden. The law does allow genetic intervention for medical purposes, such as cloning a healthy organ for donation. However, specific clinical research proposals would only be allowed to proceed if safety and efficacy could be established, and if the Health Minister deemed them not to violate human dignity. The Health Minister will be responsible for deciding how to supervise such intervention. Violation of the ban is punishable by two years in prison (Bashi, 1998).

Interestingly, the law does not specifically say that human genetic intervention is opposed to human dignity. During the ban, the law states that the Supreme Helsinki Committee will act as an advisory committee "to follow developments in medicine, science, and biotechnology in the sphere of genetic experimentation on human beings, and to report annually, advise, and make recommendations to the Health Minister as to how to proceed, to continue as is, or to reformulate the law" (Fishman, 1999).

Malaysia

The Malaysian Cabinet has banned the cloning of human beings because it is "against nature" (Reuter, 1997a). The cloning of human beings was seen as unethical and an interference with God's creation. However, cloning of animals is allowed for scientific purposes.

Peru

Peru was the first Latin American nation to ban human cloning in a new General Health Law passed by Congress on June 12, 1997 (Reuter, 1997b). The Congress' health committee found that cloning of human beings goes against people's individuality. The law's aim is to avoid "creating unnatural procreation."

Countries with Proposed Legislation to Prohibit Cloning

Argentina, Belgium, Canada, China, Japan, and South Korea have proposed legislation but have not yet passed laws to prohibit the cloning of human beings. Until Canada passes legislation, cloning of human beings is subject to a voluntary moratorium introduced by the Minister of Health in July 1995. Even though China and Japan have not yet passed legislation, the Chinese Minister of Health and the Japanese Education Ministry have stated that they will not provide funding for research on cloning human beings. South Korea's Ministry of Health and Social Welfare has proposed an expansion of existing rules that ban the implantation of

genetically engineered human embryos to include a prohibition on human cloning. In Argentina and Belgium, legislation to regulate the cloning of human beings is also being considered.

Canada

In its final report, the Royal Commission on New Reproductive Technologies concluded, that "certain activities conflict so sharply with the values espoused by Canadians and by this Commission, and are so potentially harmful to the interests of individuals and of society, that they must be prohibited by the federal government under threat of criminal sanction". These activities include human zygote/embryo research related to ectogenesis, cloning, animal/human hybrids, and the transfer of zygotes to another species.

Based on the recommendations of the Royal Commission, Canada proposed a comprehensive national policy on the management of human reproductive and genetic technologies in June, 1996. The *Human Reproductive and Genetic Technologies Act* would have prohibited 13 unacceptable uses of new reproductive and genetic technologies, including cloning of human embryos, germ-line genetic alteration, and other practices that commercialize reproduction and are contrary to the principles of human dignity, respect for life and protection of the vulnerable. However, the legislation died on the order paper in April 1997, leaving all research and experiments in Canada subject to a voluntary moratorium introduced by the Minister of Health in July 1995.

On October 9, 1997, Bill C-247, An Act to amend the Criminal Code by adding a section on genetic manipulation, was introduced into the House of Commons as a Private Member's Bill.[7] Bill C-247 criminalizes human cloning and germ-line genetic alteration without prohibiting beneficial scientific research in genetics. The bill states that

> "No person shall knowingly
> (a) manipulate an ovum, zygote or embryo for the purpose of producing a zygote or embryo that contains the same genetic information as a living or deceased human being or a zygote, embryo or foetus, or implant in a woman a zygote or embryo so produced; or
> (b) alter the genetic structure of an ovum, human sperm, zygote or embryo if the altered structure is capable of transmission to a subsequent generation."

Violation of the above prohibitions would be a criminal offense punishable by a fine of up to $500,000, imprisonment for up to ten years, or both. This bill was still being considered by the House of Commons as late as February 1999 (Hansard, 1999).

In addition, a group composed of three of Canada's major funding bodies, the Medical Research Council, the Natural Sciences and Engineering Research Council, and the Social Sciences and Humanities Research Council, issued a policy statement entitled the "Tri-Council Policy

---

[7] Private Members' Public Bills, sponsored by a private Member who is not a Minister of the Crown, are public policy initiatives that affect the entire general public or a portion thereof.

Statement: Ethical Conduct for Research Involving Humans" in August, 1998 (Tri-Council, 1998). This policy statement describes standards and procedures for governing research involving human subjects. Included in the policy statement is a section on "Research Involving Human Gametes, Embryos or Foetuses," Article 9.5 of which states:

> "It is not ethically acceptable to undertake research that involves ectogenesis, cloning human beings by any means including somatic cell nuclear transfer, formation of animal/human hybrids, or the transfer of embryos between humans and other species."

While these policies only apply to research funded by these three Councils, application of these policies to privately funded research is being considered.

China

In May 1997, the Chinese Academy of Sciences, China's leading institute of scientific research, banned the cloning of human beings, and called for a committee to set standards for cloning animals (Associated Press, 1997). In response to strong objections to human cloning by both scientists and the Chinese government, legislation similar to that currently being implemented in Hong Kong will probably soon be passed (Becker, 1997). The new *Human Reproductive Technology Bill* will prohibit the cloning of any human embryo, and specifically outlaw cloning by nuclear transfer (Becker, 1997). In Hong Kong, a statutory monitoring committee has been set up together with an ethics committee to exercise tight control of reproductive technology, and a similar body comprising scientists, ethicists, and government agencies has been strongly advocated in mainland China (Becker, 1997). Meanwhile, the Chinese Minister of Health has emphasized the "Policy of the Four Nos" towards research on human cloning — No support; No approval; No license; No acceptance (Becker, 1997).

Japan

The Japanese Science Council, an advisory panel of the Ministry of Education, Science, Sports, and Culture, has announced that it will introduce strict controls on cloning research carried out at universities and national research institutes. Regulations will restrict the application of techniques, such as somatic cell transfer to nonhuman cells, and all cloning projects will have to undergo scrutiny by a committee of experts in ethics, medicine, and law. The Education Ministry had previously announced in March 1997 that it would not provide funding for scientific research on cloning human beings. In addition, the Council for Science and Technology, the country's principal science policy body, is proposing a legal ban on human cloning in all institutions, but is soliciting public opinion before making a final announcement (Saegusa, 1998).

South Korea

In response to the December 1998 announcement by Korean scientists of the cloning of a human embryo, politicians are working to expand the 1997 rules adopted by the Ministry of

Health and Social Welfare that cover genetic research that bans the implantation of genetically engineered human embryos, but not human cloning (Baker, 1999). Therefore, South Korea's Parliament is now considering legislation to ban cloning of human cells except for disease research (Baker, 1999). One proposal before the National Assembly gives the task of reviewing such experiments to a committee of representatives from government, religious groups, research and industry (Baker, 1999).

Argentina and Belgium

Argentina has proposed legislation that is intended to deter efforts to clone human beings using somatic cell nuclear transfer. In Belgium, legislation covering medical ethics including cloning is currently being considered by parliament (HGAC and HFEA, 1998b).

Table 7. Legislation in Other Countries Prohibiting Cloning of Human Beings[8]

COUNTRY	LAW	DATE	SYNOPSIS
Argentina		(proposed)	Intend to deter efforts to clone human beings using somatic cell nuclear transfer.
Victoria, Australia	Infertility Treatment Act	1995	Bans cloning of human beings.
South Australia	Reproductive Technology Act	1988	Bans cloning of human beings.
Western Australia	Human Reproductive Technology Act	1991	Bans cloning of human beings.
Austria	Federal Law on Medically Assisted Procreation	1992	Implicitly prohibits cloning of human beings.
Belgium		(proposed)	Legislation covering medical ethics including cloning is currently being considered by Parliament.
Canada	An Act to amend the Criminal Code (genetic manipulation) (Bill C-247)	(proposed)	Would criminalize human cloning and germ-line genetic alteration without prohibiting beneficial scientific research in genetics.
China	Human Reproductive Technology Bill	(proposed)	Intend to deter efforts to clone human beings using somatic cell nuclear transfer.
Denmark	Scientific Ethical Committee System and the Handling of Biomedical Research Projects (Act No. 503)	1992	Research on cloning (production of genetically identical individuals) is forbidden, as is nuclear substitution.
Denmark	Medically Assisted Procreation in Connection with Medical Treatment, Diagnosis and Research (Act No. 460)	1997	Confirms the Danish Parliament's position of Jan. 25, 1995, that treatment can not be initiated in areas where a research ban already exists under the 1992 Act.
France	Federal Bioethics Legislation (Laws 94-653 and 94-654)	1994	Implicitly prohibits human cloning. Bioethics Committee recommended that the ban should be made more explicit when the bioethics legislation is revised in 1999.
Germany	Federal Embryo Protection Act	1990	The creation of an embryo genetically identical to another embryo, fetus or any living or dead person is an offense.

[8] From: Human Genetics Advisory Commission (HGAC) and Human Fertilisation and Embryology Authority (HFEA). 1998b. "Cloning Issues in Reproduction, Science and Medicine." Issued December 1998; and Knoppers, B. 1997. Cloning: An International Comparative Perspective. *In:* Cloning Human Beings: Report and Recommendations of the National Bioethics Advisory Commission, Volume II, June, 1997.

Table 7. Legislation in Other Countries Prohibiting Cloning of Human Beings (continued)

COUNTRY	LAW	DATE	SYNOPSIS
Israel	Anti-genetic Intervention Law	1998	Places a five year moratorium on any attempt to clone human beings or create a human being through germ-line gene therapy. Does not prohibit research and development of cloning technologies.
Japan		(proposed)	A Committee of the Council for Science and Technology is discussing ways of regulating human cloning.
Malaysia		1997	Bans the cloning of human beings.
Norway	Medical Use of Biotechnology (Law No. 56)	1994	Implicitly prohibits embryo cloning.
Peru	General Health Law	1997	Prohibits human cloning.
Slovakia	1994 Health Care Law	1994	Implicitly prohibits embryo cloning.
South Korea		(proposed)	Legislators want to ban all human cloning experiments except those that relate to disease research. A proposal before the National Assembly creates a committee of representatives from government, religious groups, research, and industry.
Spain	Spanish Civil Code - Assisted Reproduction Procedures (Law No. 35/1988)	1988	Explicitly prohibits embryo and oocyte cloning with criminal sanctions.
Sweden	Measures for the Purposes of Research or Treatment in Connection with Fertilized Human Oocytes (Law No. 115)	1991	Implicitly prohibits embryo and oocyte cloning with criminal sanctions.
Switzerland	Law on Reproductive Medicine in Humans	1990	prohibits interventions on the genetic material of gametes, live embryos, and fetuses; prohibits measures aimed at influencing the sex or inherited characteristics of the unborn child; prohibits use of live embryos, fetuses, and parts thereof for research purposes; and prohibits cloning, creation of chimeras, interspecies hybridization, and extracorporeal procreation.
Switzerland	Amendment of Federal Constitution	1992	Legally binding, implicitly prohibits embryo cloning.
Switzerland	Federal Bill on Medically Assisted Procreation	1996	Proposes criminal sanctions for the artificial creation of genetically identical beings.
United Kingdom	Human Fertilisation and Embryology Act	1990	The nuclear substitution of an embryo, or any cell while it forms part of an embryo is expressly prohibited.

UPDATE ON POLICY STATEMENTS AND ETHICAL GUIDELINES OF INTERNATIONAL ORGANIZATIONS

The possibility of cloning human beings has prompted responses from several international organizations. The Council of Europe, the World Health Organization (WHO), UNESCO's International Bioethics Committee (IBC), the Human Genome Organization (HUGO), the European Commission's bioethics advisory panel, and the Denver Summit of Eight[9] have all called for a worldwide ban on the cloning of human beings (Table 8). The policy statements of these international organizations are detailed below.

Council of Europe

On April 4, 1997, 21 countries[10] associated with the Council of Europe signed an international convention, the *Convention for the Protection of Human Rights and Dignity with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*, which calls for a ban on human cloning (Council of Europe, 1997). In addition, Article 13 of the *Convention on Human Rights and Biomedicine* prohibits interventions seeking to introduce any modification in the genome of any descendants and therefore, implicitly, forbids cloning of human beings including by use of somatic (non-reproductive) cells (Council of Europe, 1997). The Convention is open for signature to the Council's 40 member countries as well as Australia, Canada, Japan, the United States and the Holy See, which contributed to the drafting process. This text represents the first binding legal instrument ever drafted on an international scale with a view to safeguarding human dignity and fundamental rights against any improper applications of medicine and biology.

On January 12, 1998, representatives from 19 members of the Council of Europe signed an *Additional Protocol to the Convention on Human Rights and Biomedicine on the Prohibition of Cloning Human Beings* that committed their countries to prohibiting by law "any intervention seeking to create human beings genetically identical to another human being, whether living or dead" (Council of Europe, 1998). The Protocol is limited to a ban on the cloning of human beings by embryo splitting or nuclear transfer. It does not prohibit the cloning of cells and it does not deal with the use of embryonic stem cells. The Protocol was not signed by two European countries. Germany claimed that the measure was weaker than a current German law that forbids all research on human embryos (Schuman, 1998). The United Kingdom did not sign because of its strong tradition of defending the freedoms of scientific research (Schuman, 1998). Initially, the Netherlands also refused to sign the Protocol. However, following a debate in the Lower House

---

[9] In addition to the original G7 leaders from the world's leading industrialized countries, Britain, Canada, France, Germany, Italy, Japan and the United States, the 1997 Denver Summit of the Eight also included Russia.

[10] Denmark, Estonia, Finland, France, Greece, Iceland, Italy, Latvia, Lithuania, Luxembourg, The Netherlands, Norway, Portugal, Romania, San-Marino, Slovakia, Slovenia, Spain, Sweden, Turkey, and Macedonia. (http://www.coe.fr/oviedo/index.htm)

of the Dutch Parliament, the Dutch government decided to sign the Protocol with the caveat that the term "human being" be defined as humans who are already born (Gordijn, 1999). The other countries that signed were Denmark, Estonia, Finland, France, Greece, Iceland, Italy, Latvia, Luxembourg, Moldova, Norway, Portugal, Romania, San Marino, Slovenia, Spain, Sweden, Macedonia and Turkey.

World Health Organization

On March 11, 1997, Dr. Hiroshi Nakajima, the Director-General of the World Health Organization (WHO), issued a statement condemning human cloning:

> "WHO considers the use of cloning for the replication of human individuals to be ethically unacceptable as it would violate some of the basic principles which govern medically assisted procreation. These include respect for the dignity of the human being and protection of the security of human genetic material" (WHO, 1997a).

However, other uses of cloning technology, such as animal cloning and the routine cloning of human DNA, genes and cells, should not be banned (WHO, 1997a). These uses of cloning technology hold the promise of advancing biomedical research on the diagnosis and treatment of diseases such as cancer, heart disease and diabetes.

In his statement, the Director-General also referred to the guiding principles set forth in 1992 by the scientific group convened by the Special Programme of Research, Development and Research Training in Human Reproduction. The role of this group was to review the technical aspects of medically assisted procreation and related ethical issues. The group upheld "the right of everyone to enjoy the benefits of scientific progress and it applications" and the need "to respect the freedom indispensable for scientific research and creative activity" (WHO, 1997a). They also stressed that "there is a universal consensus on the need to prohibit extreme forms of experimentation, such as human cloning, interspecies fertilization, the creation of chimeras and, at present, the alteration of germ-cell genome" (WHO, 1997a).

In May 1997, at the meeting in Geneva, the Fiftieth World Health Assembly adopted a resolution affirming that "the use of cloning for the replication of human individuals is ethically unacceptable and contrary to human integrity and morality" (WHO, 1997b). The Director-General was asked to clarify the potential applications of cloning procedures in human health and their ethical, scientific and social implications. This resolution was affirmed and upheld in 1998 at the Fifty-first World Health assembly (WHO, 1998).

In October 1998, a small working group of independent and government experts met at WHO headquarters to consider a report containing a first draft of guiding principles and recommendations to WHO and its Member States entitled *Cloning in Human Health* (WHO, 1999). The draft guiding principles were inspired by the basic principles of medical ethics, including beneficence, non-maleficence, confidentiality, autonomy, equity and access to care for all, and were based on fundamental values such as dignity, human rights and freedom (WHO, 1999). The draft guiding principles included subjects such as the need for public education on

genetic research, the interaction of genes and the environment, the right to retain control over one's genetic material and the information derived from it, and gene therapy (WHO, 1999).

The United Nations Economic, Scientific and Cultural Organisation

The *Universal Declaration on the Human Genome and Human Rights* was formulated in December 1996 by the United Nations Economic, Scientific and Cultural Organisation (UNESCO) International Bioethics Committee (IBC). The Declaration received widespread support and was unanimously adopted on November 11, 1997, by UNESCO's 186 member States. On November 19, 1998, the 86 member countries of the United Nations Commission on Human Rights approved the Declaration, and on December 9, 1998, it was adopted by the United Nations General Assembly.

Article 11 of the Declaration addresses the issue of cloning of human beings. Article 11 states:

> "Practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted. States and competent international organisations are invited to co-operate in identifying such practices and in determining, nationally or internationally, appropriate measures to be taken to ensure that the principles set out in this Declaration are respected" (UNESCO, 1997).

Human Genome Organization

In March 1996, about a year before Dolly was cloned, the International Ethics Committee of the Human Genome Organization (HUGO) issued the *Statement on the Principled Conduct of Genetic Research* (HUGO, 1996). The Statement is concerned with research under the Human Genome Project and Human Genome Diversity Project. In its background principles, the Statement refers to the "acceptance and upholding of human dignity and freedom." Cloning of human beings would violate these principles. In addition, the cloning of a human being would violate a principle referred to in the Statement's preamble that is concerned with the "reduction of human beings to their DNA sequences and attribution of social and other human problems to genetic causes."

In March 1999, the HUGO Ethics Committee issued its *Statement on Cloning* that makes specific recommendations on both animal and human cloning (Chadwick, 1999). The recommendations on human cloning are subdivided according to the purposes for which the cloning is carried out, reproductive cloning, basic research, and therapeutic cloning (Chadwick, 1999). The HUGO Ethics Committee makes the following recommendations:

- *Animal Cloning.* Animal cloning should be subject to the same principles for animal welfare as other experimentation on animals, and possible consequences on biodiversity should be considered.

- *Reproductive Cloning.* There should be no attempt to produce a genetic "copy" of an existing human being by somatic cell nuclear transfer. However, the use of somatic cell nuclear transfer may be supported if it is used to avoid a disease, such as an error in mitochondrial DNA.
- *Basic Research.* In both humans and animals, cloning techniques should be supported to investigate a wide variety of scientific questions, including the study of gene expression and the study of aging.
- *Therapeutic Cloning.* Research to produce cells and tissues for therapeutic transplants should be supported.

HUGO also states that the creation of human embryos should be considered for certain types of research that may be of widespread benefit to humanity, such as the development of embryonic stem cells (Chadwick, 1999).

European Commission

In June, 1997 at a meeting at the Hague, the European Commission's bioethics advisory panel called human cloning ethically unacceptable and said it should be prohibited by law (Herman, 1997). The bioethics panel also specifically rejected the idea of embryo splitting in order to increase the success rate of IVF. However, the panel did recognize that cloning research might have important therapeutic implication such as in the study of aging and cancer, or the development of stem cells that could be used to repair or regenerate human organs. However, the European Commission must leave legislation against such experiments up to its individual member nations.

The Denver Summit of the Eight

The Denver Summit of the Eight concluded their 23rd annual summit calling for specific actions on a host of economic, global and political issues. The 18-page final communiqué, issued June 22, 1997, included a specific article related to cloning. Article 47 of the communiqué states that the G8 "agree on the need for appropriate domestic measures and close international cooperation to prohibit the use of somatic cell nuclear transfer to create a child" (Denver Summit of the Eight, 1997).

Table 8. Policy Statements and Ethical Guidelines of International Organizations

ORGANIZATION	POLICY/GUIDELINE	DATE	SYNOPSIS
Council of Europe	Additional Protocol to the Convention on Human Rights and Biomedicine on the Prohibition of Cloning Human Beings	January 1998	Prohibits any intervention seeking to create human beings genetically identical to another human being, whether living or dead.
World Health Organization (WHO)	Resolution on Human Cloning (WHA50.37)	1997	Affirmed that the use of cloning for the replication of human individuals is ethically unacceptable and contrary to human integrity and morality.
UNESCO's International Bioethics Committee (IBC)	Universal Declaration on the Human Genome and Human Rights (29 C/Resolution 17)	November 1997	Prohibits practices which are contrary to human dignity, such as reproductive cloning of human beings.
Human Genome Organization (HUGO)	Statement on cloning	March 1999	States that there should be no attempt to produce a genetic "copy" of an existing human being by somatic cell nuclear transfer.
European Commission	Meeting at the Hague	June 1997	Called human cloning ethically unacceptable and should be prohibited by law.
Denver Summit of the Eight	Communique: The Denver Summit of the Eight	June 1997	The heads of state for the United States, Japan, Germany, England, France, Italy, and Canada, endorsed a worldwide ban on human cloning.

CONCLUSIONS

The cloning of Dolly has paved the way for major advances in biotechnology, reproductive medicine, and cell-based therapies. In the last two years, since the cloning of Dolly, there have been several scientific advances. The ability to clone mammals other than sheep from adult cells has been reported for cows and mice (Kato, 1998; Wakayama, 1998). In addition, techniques have been developed to produce cloned animals carrying specific genes, providing an efficient means for producing genetically engineered animals that can make proteins in their the milk that could then be used for pharmaceutical or clinical purposes (Schnieke, et al., 1997; Fitzgerald, 1998). The last cow of a rare breed has been cloned in an effort to save the breed from extinction (Weiss, 1998d), and scientists are preparing to clone other rare and endangered animals (Farley, 1998). Nuclear transfer technology has also been used for human applications, including in preimplantation diagnosis during IVF (Cohen, 1998), to try to treat infertility (Weiss, 1998f), and in an attempt to produce human embryonic stem cells (Wade, 1998). Many of these advances hold the promise of improved treatments for diseases for which there are currently no good alternatives.

Scientists are just beginning to explore the potential future uses of somatic cell nuclear transfer cloning. Before long, the preservation of genetically important strains and mutants of laboratory and farm animals, the preservation and propagation of rare and endangered species, and the unlimited multiplication of elite animals from selected matings will be routine. By combining cloning technology with transgenic techniques, the precise and efficient genetic modification of farm animals will be possible. By genetically engineering cloned animals to express human proteins (e.g. histocompatiliblity antigens) on the surface of cells and organs, the risk of immune rejection in xenotransplantation may be significantly reduced. In addition, cloning technology may lead to the development of customized (e.g. autologous) human embryonic stem cells for use as cell and tissue-based therapies that would not be rejected by the patient's immune system.

While cloning techniques may one day provide improved treatments for diseases, revolutionize the production of biopharmaceuticals, and save endangered species, mammalian cloning does have its risks. In addition to high rates of spontaneous abortion late in pregnancy and death soon after birth, mammalian cloning has been linked to a developmental defect of the immune system and may be associated with premature aging. Thus, the question of safety remains, and casts doubt on the future uses of mammalian cloning.

Beyond the safety concerns, the prospect of cloning human beings raises several other ethical concerns. These concerns have prompted calls for worldwide bans. Consequently, language that directly prohibits the use of federal funds for cloning of human beings was included in appropriations legislation that prohibits the use of federal funds for human embryo research. In addition, five states have enacted legislation prohibiting cloning of human beings. The FDA has also asserted its authority to regulate the cloning of human beings. Similarly, several other

nations and international organizations have also enacted laws or issued policy statements prohibiting the cloning of human beings.

There appears to be broad international agreement that cloning of human beings for reproductive purposes should be prohibited. However, there is less agreement as to whether or not the use of cloning technology to develop novel therapeutic applications should be allowed. Some of the legislation and policies have specifically recognized the potential benefits of the use of cloning technology for therapeutic purposes. However, other policies are very broad and essentially prohibit any use of somatic cell nuclear transfer using human cells.

It is clear that the potential benefits that may be realized through the use of cloning technology are many. However, the potential for cloning a child is an issue that we will be grappling with for a long time to come. Therefore, responsible public policy will need to be crafted in such a way as to prevent the use of cloning technology for purposes for which it is found to be ethically unacceptable, while allowing for beneficial uses that hold so much promise for curing human diseases.

REFERENCES

Australian Academy of Sciences (AAS). 1999. On Human Cloning: A Position Statement. February 4.

Andrews, L. 1997. The Current and Future Legal Status of Cloning. *In:* Cloning Human Beings: Report and Recommendations of the National Bioethics Advisory Commission, Volume II, June, 1997.

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

Associated Press. 1997. China Bans Human Cloning. May 12.

Associated Press. 1999. Dolly Had Three Little Lambs. April 1.

Australian Health Ethics Committee (AHEC) of the National Health and Medical Research Council. 1998. Scientific, Ethical and Regulatory Considerations Relevant to Cloning Human Beings. December.

Baguisi, A., Behboodi, E., Melican, D. T., Pollock, J. S., Destrempes, M. M., Cammuso, C., Williams, J. L., Nims, S. D., Porter, C. A., Midura, P., Palacios, M. J., Ayres, S. L., Denniston, R. S., Hayes, M. L., Ziomek, C. A., Meade, H. M., Godke, R. A., Gavin, W. G., Overstom, E. W., and Echelard, Y. 1999. Production of goats by somatic cell nuclear transfer. *Nature Biotechnology* **17:** 456-461.

Baker, M. 1999. Korean Report Sparks Anger and Inquiry. *Science* **283:** 16-17.

Bashi, S. 1998. Israel Bans Genetic Cloning. *The Associated Press* Wednesday, December 30.

BBC. 1999. Scientists clone a goat. *BBC News Online* Monday, April 26.

Becker G. K. 1997. Cloning Humans? The Chinese Debate and Why It Matters. *Eubios Journal of Asian and International Bioethics* **7:** 175-8.

BNA. 1998. FDA Affirms Authority to Regulate Human Cloning Involving Nuclear Transfer. *The Bureau of National Affairs* **3(13)**, January 21.

Butler, D. 1997. France is urged to loosen ban on embryo research. *Nature* **387:** 218.

Campbell KH, McWhir J, Ritchie WA, Wilmut I. 1996. Sheep cloned by nuclear transfer from a cultured cell line. *Nature* **380:** 64-66.

Chadwick, R. 1999. HUGO Ethics Committee – Statement on cloning. *Ebios Journal of Asian and International Bioethics* **9:** 70.

Cibelli, J. B., Stice, S. L., Golueke, P. J., Kane, J. J., Jerry, J., Blackwell, C., Ponce de León, F. A., Robl, J. M. 1998. Cloned Transgenic Calves Produced from Nonquiescent Fetal Fibroblasts. *Science* **280:** 1256 - 1258.

Cohen, J., Scott, R., Schimmel, T., Levron, J., and Willadsen, S. 1997. Birth of infant after transfer of anucleate donor oocyte cytoplasm into recipient eggs. *The Lancet* **350:** 186-187.

Cohen, P. 1998. Dolly helps the infertile. *New Scientist* May 9, p. 6.

Council of Europe. 1997. *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*. European Treaty Series, No. 164, Oviedo, April 4.

Council of Europe. 1998. *Additional Protocol to the Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine, on the Prohibition of Cloning of Human Beings.* Paris, January 1.

Denver Summit of the Eight. 1997. Communique: The Denver Summit of the Eight. June 22.

Evans, M. J., Gurer, C., Loike, J. D., Wilmut, I., Schnieke, A. E., and Schon, E. A. 1999. Mitochondrial DNA genotypes in nuclear transfer-derived cloned sheep. *Nature Genetics* **23:** 90-93.

Farley, M. 1998. China Turns to Genetics in Bid to Save Its Pandas. *Los Angeles Times* Friday, September 11.

First, N. L. and Prather, R. S. 1991. Genomic potential in mammals. *Differentiation* **48:** 1-8.

Fishman, R. H. B. 1999. Israeli cloning ban endorsed by scientists. *The Lancet* **353(9148):** 218.

Fitzgerald, A. 1998. Cloned calves may aid drug research. *The Detroit News /Associated Press* Wednesday, January 21.

Gordijn, B. 1999. Professional Opinion: The Cloning of Human Beings. The Dutch Debate in an International Context. Occasional Paper Number 5 from the Centre for Professinal Ethics, University of Central Lancashire, Preston, Lancashire.

Hansard. 1999. Edited Hansard Thursday, February 11, Number 179. http://www.parl.gc.ca/36/1/parlbus/chambus/house/debates/179_1999-02-11/toc179-e.htm

Henahan, S. 1997. Monkey Business. Genentech's Access Excellence What's News: http://www.gene.com/ae/WN/SUA09/monkey397.html

Herman, R. 1997. European Bioethics Panel Denounces Human Cloning. *The Washington Post* Tuesday, June 10.

Human Genetics Advisory Commission (HGAC) and Human Fertilisation and Embryology Authority (HFEA). 1998a. Cloning Issues in Reproduction, Science and Medicine. January.

Human Genetics Advisory Commission (HGAC) and Human Fertilisation and Embryology Authority (HFEA). 1998b. Cloning Issues in Reproduction, Science and Medicine. December.

Human Genome Organization (HUGO). 1996. HUGO Statement on the Principled Conduct of Genetics Research: HUGO Ethical, Legal, and Social Issues Committee Report to HUGO Council. March. http://www.gene.ucl.ac.uk/hugo/conduct.htm

Holden, C., ed. 1997. Calf Cloned from Bovine Cell Line. *Science* **277:** 903.

Hotz, R.L. 1998. U.S. Researchers Use Cow's Egg to Clone 5 Species' Embryos. *Los Angeles Times* Monday, January 19.

International Digest of Health Legislation, 1993, Vol. 44, No. 2, pp. 256-257

Kato, Y., Tani, T., Sotomaru, Y., Kurokawa, K., Kato, J., Doguchi, H., Yasue, H., and Tsunoda, Y. 1998. Eight calves cloned from somatic cells of a single adult. *Science* **282:** 2095-2098.

Knoppers, B. 1997. Cloning: An International Comparative Perspective. *In:* Cloning Human Beings: Report and Recommendations of the National Bioethics Advisory Commission, Volume II, June, 1997.

Kolata, G. 1999. Cloned Sheep Showing Signs of Old Cells, Report Says. *The New York Times* Thursday, May 27.

Lederer, E. M. 1998. Dolly the clone now Dolly the mom. *The Associated Press* Friday, April 24.

Lemonick, M.D. 1998. Dolly, You're History. *Time*, August 3, p. 64-65.

Meng, L., Ely, J. J., Stoufer, R. L., and Wolf, D. P. 1997. Rhesus monkeys produced by nuclear transfer. *Biol Reprod* **57(2):** 454-459.

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

Newswire. 1998. Cloning made easy. *New Scientist* **160(2160):** 27.

PCT/U397/12919. 1997. Embryonic or Stem-Like Cell Lines Produced by Cross Species Nuclear Transplantation. *International Application Published Under the Patent Cooperation Treaty* WO 98/07/841.

Pennisi, E. 1997. Transgenic Lambs From Cloning Lab. *Science* **277:** 631.

Price, E. C. 1998. Does the FDA Have Authority to Regulate Human Cloning? *Harvard Journal of Law and Technology* **11(3):** 619-641.

Renard, J. -P., Chastant, S., Chesne, P., Richard, C., Marchal, J., Cordonnier, N., Chavatte, P., and Vignon, X. 1999. Lymphoid hypoplasia and somatic cloning. *The Lancet* **353:** 1489-1491.

Reuter. 1997a. Malaysia Bans Human Cloning. *Reuter* March 19.

Reuter. 1997b. Peru Outlaws Human Cloning. *Reuter* June 14.

Saegusa, A. 1998. Japan to Ban Human Cloning. *Nature Medicine* **4(9):** 993.

Schnieke, A. E., Kind, A. J., Ritchie, W. A., Mycock, K., Scott, A. R., Ritchie, M., Wilmut, I., Colman, A., Campbell, K. H. S. 1997. Human Factor IX Transgenic Sheep Produced by Transfer of Nuclei from Transfected Fetal Fibroblasts. *Science* **278:** 2130 - 2133.

Schuman, J. Europe Signs Human Cloning Ban. *The Associated Press* Monday, January 12.

Sgaramella, V. and Zinder, N.D. 1998. Dolly Confirmation. *Science* **279:** 635-636.

Shiels, P. G., Kind, A. J., Campbell, K. H. S., Waddington, D., Wilmut, I., Colman, A., and Schnieke, A. E. 1999. Analysis of telomere lengths in cloned sheep. *Nature* **399:** 316-317.

Signer, E. N., Dubrova, Y. E., Jeffreys, A. J., Wilde, C., Finch, L. M. B., Wells, M., and Peaker, M. 1998. DNA fingerprinting Dolly. *Nature* **394:** 329 - 330.

Tanne, J. H. 1999. Dolly's other DNA came from donor egg. *BMJ* **319:** 593.

Tri-Council Policy Statement. 1998. Ethical Conduct for Research Involving Humans. August.

UNESCO. 1997. *Universal Decleration on the Human Genome and Human Rights*. December 3.

Wade, N. 1998. Human Cells Revert to Embryo State, Scientists Assert. *The New York Times* November 12.

Wakayama, T., Perry, A.C.F., Zuccotti, M., Johnson, K.R., and Yanagimachi, R. 1998. Full-term development of mice from enucleated oocytes injected with cumulus cell nuclei. *Nature* **394:** 369-374.

Wakayama, T. and Yanagimachi, R. 1999. Cloning of male mice from adult tail-tip cells. *Nature* Genetics **22:** 127-128.

Weiss, R. 1998a. Researchers Report Creating Cloned Human Embryos. *The Washington Post* Thursday, December 17, page A3.

Weiss, R. 1998b. Cow Eggs Play Crucial Role in Cloning Effort. *The Washington Post* Monday, January 19, page A1.

Weiss, R. 1998c. Japanese Clone 8 Calves From One Adult Cow. *The Washington Post* Wednesday, December 9, page A1.

Weiss, R. 1998d. Last Cow of Rare Breed is Cloned in New Zealand. *The Washington Post* Thursday, August 20, page A2.

Weiss, R. 1998e. Cloned Calves Are 'Major Step' Toward Making Medicines in Milk. *The Washington Post* Wednesday, January 21, page A3.

Weiss, R. 1998f. Fertility Process Moves Genes Egg to Egg. *The Washington Post* Friday, October 9, page A1.

Weiss, R. 1999. Failure in Monkeys Hints at Human Cloning Snags. *The Washington Post* Friday, January 29, page A2.

World Health Organization (WHO). 1997a. WHO Director-General Condemns Human Cloning. Press Release WHO/20, March 11. http://www.who.ch/press/1997who20.html

World Health Organization (WHO). 1997b. World Health Assembly States Its Position on Cloning in Human Reproduction. Press Release WHA/9, May 14. http://www.who.ch/press/1997/wha9.html

World Health Organization (WHO). 1998. Ethical, Scientific and Social Implications of Cloning in Human Health. Fifty-First World Health Assembly, WHA51.10, Agenda item 20, May.

World Health Organization (WHO). 1999. Cloning in Human Health: Report by the Secretariat. Fifty-Second World Health Assembly A52/12, Provisional agenda item 13, April.

Wilmut, I., Schnieke, A. E., McWhir, J., Kind, W. A. J., Campbell, K. H. S. 1997. Viable offspring derived from fetal and adult mammalian cells. *Nature* **385:** 810-813.

WuDunn, S. 1998. South Korean Scientists Say They Cloned a Human Cell. *The New York Times* December, 17.