Perfect Copy?
Law and Ethics of Reproductive Medicine

Edited by
Judit Sándor

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ISBN 978-963-9776-75-3

Copyediting: Arton Vidal
Design and typesetting: Zsolt Sándor
Printed in Hungary by FOM kft.

Center for Ethics and Law in Biomedicine
Central European University
2009 Budapest

Center for Ethics and Law in Biomedicine
Budapest 2009

Introduction

Judit Sándor

"It is the copying that originates."[1] (Clifford Geertz)

"How comes it that we all start out Originals and end up Copies?" asked once the great literary critic, Lionel Trilling, citing a lamenting eighteenth-century aesthetician. To this question, the cultural anthropologist, Clifford Geertz came up with the reassuring answer quoted above. The uniqueness of the human being has been long a preoccupation of Western philosophers, but it is true that lay people seldom contemplate the existential quandaries of the relationship between the original and the copy. Trilling also noted that authenticity only becomes an issue after a doubt arises[2] and, similarly, originality becomes important when a convincing copy emerges and threatens its unique status. It is not surprising, then, that the birth of Dolly the sheep in 1997 provoked agitated responses. Suddenly, politicians around the world sensed that cloning a human being would be the next logical step and immediately took action: international organizations and national governments issued declarations and adopted laws one after the other to prohibit the cloning of human embryos. Yet, twelve years later, we may say that the relationship between the original and the copy has become immensely more complicated, and the wide variety of cloning techniques that involve nuclear transfer and the creation of embryonic stem cell lines now provoke quite diverse moral reactions among the general public.

The title of this book, *Perfect Copy?*, including the question mark at the end of it, refers to the uncertainties concerning the terminology and efficacy of various forms of regenerative medicine today: 'cloning', 'therapeutic cloning', 'nuclear transfer', 'nuclear transplantation', and 'stem cell research'. Copying cells and creating immortal stem cell lines give us the hope to offer effective medical treatment to certain severe diseases. Making biological copies may result in creating a form of *biovalue*, "a surplus value of vitality and instrumental knowledge which can be placed at the disposal of the human subject."[3] Since this surplus value is produced from "marginal forms of vitality"[4], such as abandoned biological tissues, one might claim that otherwise useless biological waste is transformed into commercial value, and what is more important, into

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[1] Clifford Geertz, Making Experiences, Authoring Selves, in Victor W. Turner and Edward M. Bruner (eds.) *The Anthropology of Experience* (Urbana: University of Illinois Press, 1986), 373–380, at 380.

[2] Lionel Trilling, *Sincerity and Authenticity* (Cambridge: Harvard University Press, 1972).

[3] Catherine Waldby, *The Visible Human Project: Informatic Bodies and Posthuman Medicine* (London and New York: Routledge, 2000), p. 19. See also Catherine Waldby, Stem Cells, Tissue Cultures and the Production of Biovalue, *Health: An Interdisciplinary Journal for the Social Study of Health, Illness and Medicine*, 2002, 6(3): 305–323.

[4] Waldby, *The Visible Human Project*, 19.

new health value. Thus, unlike in the cases of reproductive cloning, this form of duplicating human cells and using them as building blocks for treatment is not necessarily associated with wrongful practices. Therefore, it has become necessary to reconsider some traditional ethical conceptions on prohibiting certain uses of the human body. Ethical debates on cloning and stem cell research are now concerned not only with the nature of human life and its beginnings but also with identifying "acceptable strategies for controlling the creation and development of human life."[5]

Cloning in Popular Imagination

Cloning, nevertheless, remains a provocative term and the intentional creation of genetically (almost entirely) identical human beings incite radical reactions among the general public. Many people were captivated by the technique long before it was possible to pursue, and this party originates in the influence of literary imagination. Of all literary works, perhaps Aldous Huxley's *Brave New World*[6] is the most widely known. The novel describes the infamous Bokanovsky Process, a fictional procedure in which the egg is "stimulated to split" in order to create no less than ninety-six embryos by multiplying. In Ira Levin's 1976 novel, *The Boys from Brazil*[7], "Dr. Mengele" is able to produce ninety-four clones of Adolf Hitler, while in Fay Weldon's 1989 novel, *The Cloning of Joanna May*, a cheated, disappointed husband is able to secretly produce four cloned copies of his unfaithful wife.[8] And the list could go on. In popular imagination, therefore, cloning is used for reproductive purposes and it is understood, rather simplistically, as the creation of perfect copies that are identical with the original.

The possibility of creating clones, or 'playing God' in the interpretation of religious ethicists and theologians, was always treated with suspicion. But when Dolly the sheep was born in 1997, this lingering suspicion suddenly transformed into a moral panic. George Annas, the American bio-ethicist, proposed a noteworthy explanation for this change. He felt that the sheep raised a surprising amount of public outrage, even among scientists, because, in contrast to the mass of genetically modified animals, she was named Dolly, and thus gained a *personality*. After all, in the original scientific announcement she was not given a human name: the cloned sheep was merely listed as 6LL3.[9] Naming the sheep 'Dolly' intentionally evoked the cuteness of a toy doll, and it also indicated the cloners' willingness to take responsibility for her – in contrast to the unnamed monster created by Dr. Frankenstein.[10]

[5] Herbert Gottweis, Brian Salter and Catherine Waldby, *The Global Politics of Human Embryonic Stem Cell Science: Regenerative Medicine in Transition* (Houndmills, Basingstoke: Palgrave Macmillan, 2009), 4.

[6] Aldous Huxley, *Brave New World* (London: Chatto and Windus, 1932). The influential novel is set in London in 2540 anticipating the developments in reproductive technology with the special combination with human enhancement to change society.

[7] Ira Levin, *The Boys from Brazil*. First Edition (London: Michael Joseph, 1976).

[8] Fay Weldon, *The Cloning of Joanna May* (London: Collins, 1989).

[9] Arlene Judith Klotzko, *The Cloning Sourcebook* (Oxford and New York: Oxford University Press, 2001), 87.

[10] Popular interpretations of Mary Shelley's original romantic novel incorrectly shifted the name 'Frankenstein' from the doctor who created the monster to the creature itself.

When some thirty years ago James Watson, one of the describers of the double helix of DNA, proposed the prohibition of human cloning, nobody took his warning seriously. However, when the press started to report on the birth of Dolly, politicians reacted with surprising speed. President Clinton of the United States banned the use of federal funds for human cloning. The Pope John Paul II and President Chirac of France also expressed their clear rejection without providing any details of their reasoning. Their moves were certainly influenced by the simplistic representation of cloning in popular imagination, as well as by the moral panic surrounding the possibility of creating a living organism with soul and personality.

Cloning and Reproduction

Most of the fears about cloning originate from its interpretation as a technique to reproduce human beings. However, it is instructive to compare the specific techniques of cloning with other already accepted reproductive procedures, because this way *reproductive cloning* might be put into a new context. If we consider the recently developed technologies of reproduction (*in vitro* fertilization or IVF, intracytoplasmic sperm injection of eggs or ICSI, etc.) we can see that these procedures have become accepted and acknowledged techniques almost unnoticeably, to the extent that most people take them for granted today.

In 1978 the first test-tube baby, Louise Brown, was born. Since then a number of *in vitro* reproductive technologies have been used with great success and these are not only accepted, but are practically considered normal to demand from parents expecting a child. This belief in the technological imperative is so widespread that gynecologists tend to criticize parents who do not approach a reproductive specialist in time.

A utilitarian approach would suggest that every reproductive procedure that enhances the freedom of reproduction should be welcomed, since it increases the number of children born, and because people who once could not have children now can. At the individual level, however, things look a bit different. From the point of view of motherhood, we face new and considerably difficult procedures. The preliminary medical examinations, the lengthy hormone treatments, the removal of eggs through operation, and the return of the embryo to the mother's body disintegrate the normal process of motherhood. And here we have not even spoken of the psychological dynamics of hope and disappointment. The multiplicity of interventions in reproduction has had the effect of medicalizing the sacred experience of motherhood. Through various *in vitro* techniques, the act of insemination has been separated from conception.

We need to realize that the application of various techniques of assisted reproduction, practically without noticing it, created an increasing demand for sperm and egg donors. Among these reproductive technologies, the one in which only one reproductive cell, the egg plays a role, has emerged as scandalous. If the new techniques that separate sexuality from reproduction have been so easy for the public to accept, then why is cloning so different? Perhaps because cloning is an *asexual* form of reproduction – meaning that only one sex is represented in reproduction. An entirely hypothetical question might be asked here: Would society react with such bitterness if one could create genetic copies in a procedure using *both* reproductive cells?

Stem Cell Research

While the term 'cloning' was used for a long time to mean the application of various techniques of nuclear transfer, scientists wanted to make a clear distinction between *reproductive cloning* and *embryonic stem cell research*. Perhaps this is why, only a couple years after the moral panic generated by the birth of Dolly, political reactions to the emergence of embryonic stem cell research were much less unanimous and negative.

Cloning still has many different meanings as it refers to a set of technologies[11] as well as to the result of nuclear transfer. The very possibility of producing sources of stem cells force us to reinterpret the concept of the human body, the protection of the human embryo, and the use of human oocytes. Terminological differences and ethical concerns are manifold. For instance, what does it mean in the United Nations Declaration on Human Cloning, "all forms of human cloning?"[12] The official statements made by the delegations after the vote on the Declaration reflect a strong sense of ambiguity as to whether other forms of cloning are included beyond *reproductive cloning*.[13]

[11] The polymerase chain reaction (or PCR), for which Kary Mullis received the 1993 Nobel Prize in chemistry, provides a method for rapidly synthesizing numerous copies of a DNA molecule, thus 'amplifying' it. While copying can serve as a diagnostic tool it may result also in controversial research models as well. For instance, cloned embryos used for stem cell research attracted a significant degree of controversy. The emergence of numerous new technologies has motivated scientists to apply new communication strategies, formulate new directions in the ethical debates on the status of the human embryo, and all this, in turn, opened an entirely new chapter in thinking about the human body. No wonder that scientist made efforts to separate different types of cloning techniques from each other.

[12] The United Nations Declaration on Human Cloning of March 8, 2005 declares that "a) Member States are called upon to adopt all measures necessary to protect adequately human life in the application of life sciences; b) Member States are called upon to prohibit all forms of human cloning inasmuch as they are incompatible with human dignity and the protection of human life." United Nations Resolution No. 59/280, the official text of the Declaration is available at daccessdds.un.org/doc/UNDOC/GEN/N04/493/06/PDF/N0449306.pdf, last accessed on October 15, 2009.

[13] The official press release issued after the voting acknowledged that "[r]egretting the failure to achieve consensus, several delegations said they had voted against the text today because the reference to 'human life' could be interpreted as a call for a total ban on all forms of human cloning. The Assembly had missed an opportunity to adopt a convention prohibiting reproductive cloning, said the United Kingdom representative, because of the intransigence of those who were not prepared to recognize that other sovereign states might decide to permit strictly controlled applications of therapeutic cloning. Echoing the views of a number of speakers, he said the Declaration was a non-binding political statement, which would not affect his country's position on the issue." The statements made by the delegations of China and India also explained why they voted against the Declaration: ... "The representative of China, also speaking in explanation after the vote, said that different countries varied in their understanding of the text's inherent moral, ethical and religious aspects, and it was regrettable that the Declaration failed to give effect to the concerns of those countries. The prohibitions contained in the text could be misunderstood as covering all forms of cloning. Having voted against the Declaration, the Chinese Government would continue to adhere to its position against reproductive human cloning, while maintaining strict controls over therapeutic cloning." ... "The representative of India expressed deep regret that the Sixth Committee had been unable to recommend to the plenary a text that was acceptable to all Member States on a matter of such paramount importance as an international convention against the reproductive cloning of human beings. India had voted against the political Declaration, as some of the provisions of the Declaration could be interpreted as a call for a total ban on all forms of human cloning." See the United Nations official press release, "General Assembly approves declaration banning all forms of cloning", at www.un.org/apps/news/story.asp?NewsID=13576&Cr=cloning&Cr1, last accessed on October 15, 2009.

Over the past couple years, the debate over reproductive cloning was gradually replaced by a debate on stem cell research, and other techniques previously called *therapeutic cloning*. Stem cells are cells that generate or regenerate tissue. Stem cell lines may be described as 'perfect' in a sense as they are regarded as omnipotent tools to develop different kinds of human tissues.[14]

Breakthroughs in human embryonic stem cell (hESC) research have remained closely tied to the expansion of the *in vitro* fertilization technologies.[15] British researchers played a pioneer role in Europe in the field of stem cell research and they hoped that the permission granted for research will enable them to find treatments for Parkinson's and Alzheimer's disease, and for certain types of diabetes. Research on human embryos can be done only on stored embryos that would not otherwise be used for reproduction, and experiments are strictly to be pursued only within 14 days of conception. Therapeutic cloning is being pursued not to make a copy of a human being, but to produce organs and tissue. Since through this technique it appears that not only embryonic cells, but also adult cells can be used, the major legal concern is not the protection of embryos, but rather the need to eliminate abuses in the enormous trade in stem cells. In the 2008 Amendment of British Human Embryological and Fertilization Act numerous new therapeutic and research options were authorized, among them creation of the so called hybrid embryos.[16]

Although scientists seek to develop numerous alternatives, it seems that the fertilized zygote has the highest developmental potential as it includes *totipontent* stem cells that can generate all three embryonic germ layers. Other alternatives are the direct reprogramming of cells, such as skin cells, into cells similar to embryonic stem cells (induced *pluripotent* stem cells), or the technique of taking a single cell from an embryo and using this cell to derive embryonic stem cell lines (in this way the remaining embryo can continue to develop), or using, for this purpose, non-viable embryos that would otherwise have been discarded in the process of the IVF treatment. There are some research protocols in which nuclear transfer involves the transfer of genetic material from adult skin cells to eggs which have had the cell's nucleus removed. This can be combined with the technique so-called 'parthenogenic activation' that involves an egg being artificially stimulated by chemical or electronic means in order to make the egg start embryo development. Currently there is a new technique in which scientists use the so-called *induced pluripotent stem cells* (iPSs) that were artificially derived from a non-pluripotent cell, typically an adult somatic cell, by inducing a 'forced' expression of certain genes. These induced pluripotent stem cells are believed to be identical in many respects to natural pluripotent stem cells, such as embryonic stem cells.

Somatic stem cells have been identified in several organs in aborted fetuses and also in adults. There is no consensus about hESC research in the European Union and, as of yet, no regulation. In view of the long-term perspective, however, all ethical guidelines

[14] Social scientists and lawyers, however, often take a broader view and occupy a critical position by examining the social ethical and legal impacts of this type of research.

[15] Herbert Gottweis, *et al.*, *op. cit.*, 10.

[16] In 2006 the British Human Fertilization and Embryology Authority received applications from two different research teams for a license to derive stem cells from human embryos, created from animal eggs instead of human eggs. Before the law was modified and research was permitted, a public consultation organized and was conducted on the use of hybrid embryos.

and regulations must be applied to research sponsored by the European Union[17], whenever they involve research on human subjects. On March 29, 2007, the European Commission agreed to provide funding for the creation of a European registry for human embryonic stem cell lines.

Legal Limitations

Respect for human dignity is frequently called upon to provide reasoning against human cloning. The uniqueness of each individual is not, however, a universal value. Moreover, people are not only biological and genetic beings, but are also connected to society through unbreakable bonds that strongly determine their characters: factors such as their upbringing, their environment, their cultural background, or the age in which they are born. Among other issues, theoretical concerns related to these factors also had to be struggled with at all international forums that decided to stop human cloning.

The broad debate on the ethics of human regenerative medicine, reproduction and cloning has raised many interesting questions. By using cloning in various meanings, the general public is often left without a clear reference to what makes stem cell research techniques useful and acceptable or how are they different from reproductive cloning.

A point of reference is the Convention on Human Rights and Biomedicine, one of the most important ethical norms for biomedicine, which was adopted by the Council of Europe in 1997.[18] The first Additional Protocol to the Convention was "On the Prohibition of Cloning Human Beings."[19] The Protocol is categorical, but the reasoning behind the ban is not made clear by its text. Based on this document, all procedures aimed at creating a human being genetically identical to another, living or dead, human being are banned.[20] The Protocol determines genetically identical to mean a correlation between two human beings, the nuclei of whose cells contain identical genetic material. Thus cell and tissue cloning is not banned by the Protocol.

The Universal Declaration on the Human Genome and Human Rights[21], adopted on November 11, 1997 by the General Conference of UNESCO, is the first international

[17] Seventh Framework Programme of the European Community for Research and Technological Development (2007–2013) or FP7, see cordis.europa.eu/fp7/home_en.html.

[18] 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 (ETS No. 164); adopted in Oviedo in April 1997 and entered into force in 1999. The official text is available at conventions.coe.int/treaty/EN/Treaties/Html/164.htm, last accessed on October 16, 2009.

[19] 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 Human Beings (ETS No. 168); adopted in Paris in January 1998 and entered into force in 2001. The official text is available at conventions.coe.int/Treaty/EN/Treaties/Html/168.htm, last accessed on October 16, 2009.

[20] Article 1 of the Additional Protocol states that "1. Any intervention seeking to create a human being genetically identical to another human being, whether living or dead, is prohibited."

[21] The Universal Declaration on the Human Genome and Human Rights was adopted unanimously and by acclamation at UNESCO's 29th General Conference on 11 November 1997. The following year, the United Nations General Assembly endorsed the Declaration. The official text is available at portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION= 201.html or unesdoc.unesco.org/images/0011/001102/110220e.pdf#page=47, last accessed on October 16, 2009.

instrument which prohibits human reproductive cloning. Indeed, Article 11 of the Declaration states that: "Practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted. States and competent international organizations are invited to co-operate in identifying such practices and in taking, at national or international level, the measures necessary to ensure that the principles set out in this Declaration are respected."[22]

The mere threat of human reproductive cloning motivated some member states of the United Nations to seek the adoption of a binding international legal instrument that prohibits reproductive cloning globally. In August 2001 the Permanent Missions of France and Germany requested the Secretary-General of the United Nations to include an additional item on the agenda of the 56th Session of the General Assembly entitled "International Convention against the Reproductive Cloning of Human Beings." After years of discussion, however, instead of a convention, a legally non-binding United Nations Declaration on Human Cloning was adopted on March 8, 2005 that applies a much broader and ambiguous term – "all forms of human cloning inasmuch as they are incompatible with human dignity and the protection of human life" – instead of reproductive cloning.[23] The wording of the document left room for very different interpretations of the text, which reflected, in part, the lines of division between the different member states on this issue. The main point of contention was the question of linking the issues of reproductive and non-reproductive cloning, which was not agreeable to many States, who abstained and voted against the Declaration.

In 2007, the United Nations University Institute of Advanced Studies (UNU-IAS) produced a Report entitled *Is Human Reproductive Cloning Inevitable? Future Options for UN Governance*, which summarized up-to-date technical information on cloning, ethical issues accompanying it and the state of the art of international governance of these issues, specifically analyzing the discussions during the four years of United Nations General Assembly debate leading to the voting on the United Nations Declaration of Human Cloning. The Report expressed the view that further development of international governance would be needed and envisaged several options along this line. At its meeting in January 2008, the Bureau of International Bioethics Committee decided to include the discussion of the UNU report and the issue of human cloning and international governance into the work program of IBC for 2008–2009.

Another specialized UN agency, the World Health Organization found in its Resolution WHA51.10 of May 16, 1998 that "cloning for the replication of human individuals is ethically unacceptable and contrary to human dignity and integrity." Therefore it "urges Member States to foster continued and informed debate on these issues and to take appropriate steps, including legal and juridical measures, to prohibit cloning for the purpose of replicating human individuals."[24]

[22] See unesdoc.unesco.org/images/0011/001102/110220e.pdf#page=50, last accessed on October 16, 2009.

[23] At its 82nd meeting, the General Assembly adopted Resolution 59/280, containing in its annex the text of the United Nations Declaration on Human Cloning, by a recorded vote of 84 to 34, with 37 abstentions. See footnote 12 above and, for more information, www.un.org/law/cloning.

[24] The World Health Assembly adopted the Resolution on May 16, 1998. The official text is available at www.who.int/ethics/en/WHA51_10.pdf, accessed on October 16, 2009.

The Legal Status of 'Clone Embryos'

As long as the development of the embryo was hidden within the womb until the moment of birth, philosophical and theological perspectives dominated the formation of normative terms regarding reproduction. Aristotle believed, for instance, that personality developed along with the embryo as it gained human form. He felt that this process lasted forty days in the case of men, and eighty days for women. This concept was adopted by early canon law.

Since we have been able to observe the embryo with ultrasound and, by learning its sex, we have even been able to give it a name, our normative ideas about reproduction have come to attempt to encompass biological terms. This, naturally, is not always terribly successful, and I believe it is not even to be considered desirable in every case. Although we may consider the embryo produced by cloning to be simply a human being brought about through single-cell, sex-free reproductive procedure, it might be worthwhile to consider the fact that while this qualification is biologically correct, it does not necessarily supply us with effective legal terminology. This is not a unique case of difference between the biological and normative terminologies. According to Hungarian law, for instance, the embryo[25] comes into existence through fertilization. Fertilization – I believe – means the unification of two gametes. Accordingly, a cloned human being is not covered by this law. It is noteworthy that the law does allow for the possibility of the cloned human being to enjoy embryonic rights later because, once the embryo is implanted into the mother's womb, the law considers it to be a fetus, and thus a developing human being from the twelfth week of pregnancy.

A different conclusion can be reached from the Preamble of the Hungarian Fetal Protection Act. According to this Act No. LXXIX of December 17, 1992 on the Protection of Fetal Life, the fetus deserves protection and respect from the moment of conception. Thus conception, that is fertilization, is of significance not only for the embryo, but also the fetus. Based upon this passage one might come to the conclusion that a being that does not come into existence through fertilization is not protected by this law. Although the Hungarian law does allow research on the human embryo, provided several conditions are met, Hungary still voted in favor of prohibition of "all forms of cloning."[26]

Hasty and technology-driven lawmaking has resulted in terminological traps and

[25] According to the law, every human embryo is an embryo from the moment of fertilization to the twelfth week of pregnancy.

[26] "Hungary's representative said he voted in favor of the Declaration because it attached the utmost importance to sending a strong message that the birth of cloned human beings was not acceptable. Furthermore, during the conduct of life sciences, there was a need for a delicate balance between the freedom of research and the adequate protection of human life and dignity. Also, the Declaration was in line with the existing obligations of Hungary under international law. He hoped the Declaration was only one step in the consideration of human cloning, and not the final stage. Hungary was open for further discussions in the international community at the appropriate time." See the United Nations official press release, "General Assembly approves declaration banning all forms of cloning", at www.un.org/apps/news/story.asp?NewsID=13576&Cr=cloning&Cr1, last accessed on October 15, 2009.

legal loopholes in other jurisprudences as well. The definition of cloning in the State of South Australia contained another problem in addition to the requirement of genetic identicalness. In the Code of Ethical Research Practice of South Australia, cloning was defined as "any procedure directed at producing two or more genetically identical embryos *from the division of one embryo*" (emphasis mine).[27] Here, the reference to the "division of one embryo" covered only one method of cloning – and the application of only this type of technology is prohibited. The wording of the law did not allow to include the technique of somatic cell nuclear transfer (SCNT) which involves placing DNA from one cell into another de-nucleated cell; this is clearly not the same as dividing one embryo. Thus, South Australian scientists could continue to undertake research on cloned embryos, provided that they used only those created by SCNT.

As these examples show, the theoretical framework relevant in the prohibition of reproductive cloning (referring to the principle of respecting human dignity), is clearly not immediately applicable in the case of tissue cloning research. Therefore, it seems that the development of an internationally recognized legal dogma for therapeutic cloning procedures will take at least a couple more years.

Structure and Content of this Book

In 2007 the Center for Ethics and Law in Biomedicine invited a group of experts from different disciplines to present their view on human cloning and stem cell research. A real cross-disciplinary dialogue developed during the two days of the meeting. This book now presents the papers presented at this workshop but also some additional contributions.

The main purpose of the book is to discuss various normative answers to cloning in a comparative context. The birth of Dolly the sheep provoked a fast and almost unanimous legal reaction to reproductive cloning across the globe: a categorical ban. This provides an unprecedented case in biomedical law because this move fails to explain the reason behind a clear-cut prohibition and fails to recognize the difference between various techniques that 'copy' human cells for different purposes. Human reproductive cloning has been rejected mainly based on the arguments that it is not safe; it is not an irreplaceable technique of reproduction and copying human beings, even if they will never be identical in the strict sense of the word. The mere threat of an unsafe and ethically controversial practice resulted in the formulation of numerous international standards, ethical and legal norms in various fields of regenerative medicine. It seems that various forms of nuclear transfer are labeled as cloning and the regulation of one form of cloning cannot be viable without referring to the other forms. Moreover, one has to be aware that the same legal and technical terminology may often have diverse, even

[27] The Reproductive Technology Code of Ethical Research Practice Regulations of 1995 (SA) were established in accordance with Section 20(4) of the Reproductive Technology Act of 1988. Part I Section 2 of the Code of Ethical Research Practice provides the definition of 'cloning'. See www.aph.gov.au/House/committee/laca/humancloning/sub273.pdf, last accessed on November 13, 2009.

contradictory, cultural meanings in different countries. Therefore, this book intends to explore various cultural perspectives on the transnational debate on what was indiscriminately called "all forms of cloning" in the United Nations Declaration on Human Cloning.

The individual chapters discuss the various techniques of reproductive cloning and stem cell research, as well as the major controversies and scandals that have reshaped our conceptions about the ethical standards of conducting scientific research in the field of biomedicine and reprogenetics. *András Dinnyés*, who created Clonilla[28], the first cloned mouse in Hungary, explains and compares the various techniques of nuclear transfer that have been used, or theoretically could be used, in cloning animals. He mentions briefly the Hwang case that is more extensively analyzed by *Péter Kakuk*, a bioethicist from the University of Debrecen, Hungary, who also draws broader conclusions about the necessity of formulating and adopting internationally accepted ethical guidelines applicable in the various fields of biomedical research. He also emphasizes the importance of establishing mechanisms of social control over scientific research.

Social control would be more effective if the general public is better informed about the scientific advances in biomedical research as well as their ethical consequences. Public debates on stem cell research and human embryonic research may refer to conflicting assumptions about who will benefit from these scientific advances. *Knut W. Ruyter*, ethicist and theologian from the University of Oslo, Norway, compares the mobilization of two distinct metaphors in formulating rhetorical positions in the Norwegian public debate: "the inclusive society" and "the sorting society". The first evokes the assumption that the application of biotechnology in medical practice is for the benefit of everyone and the second refers to the threat of positive or negative selection: to the possibility of eugenism or the exclusion of certain groups of people from enjoying the benefits of science.

Two other contributions to this book discuss the ethical interpretations and legal regulations of human embryo and stem cell research in national contexts. *Orìò Ikebe*, anthropologist and bioethicist at the regional office of UNESCO in Cairo, presents the Japanese case in which the law prohibits cloning for reproductive purposes but allows for embryonic stem cell research and new government guidelines to permit therapeutic cloning are currently under preparation. Cultural attitudes concerning life and death in Japan also contribute to a relatively permissive approach towards research on human embryos. In the next chapter, *Tade Matthias Spranger*, lawyer and researcher at the Institute of Science and Ethics in Bonn, Germany, analyzes the German Stem Cell Act of 2002 which attempts to accommodate the constitutional right of scientists to conduct scientific research freely while maintaining a strong legal protection of the human embryo. Providing a prime example of research-driven legislation, the Stem Cell Act was amended in June 2008 in order to strengthen the position of scientists who are interested in stem cell research for therapeutic purposes.

Three chapters of the book discuss the most important international ethical and legal norms on human cloning and stem cell research from comparative human rights and constitutional perspectives. *Violeta Beširević*, professor of law at the Union University

[28] The first Hungarian cloned mouse was born at the end of 2006 and on January 11, 2007 gave birth to eight healthy mice.

Law School in Belgrade, Serbia, examines the possibility of moving away from the rather symbolic gestures of prohibiting reproductive cloning on the international level towards a more meaningful and grounded constitutional analysis of the applicability of the principles of human rights and fundamental liberties to the assessment of embryonic stem cell research and therapeutic cloning.

Hanne-Maaria Rentola, theologian at the University of Helsinki, Finland compares the two major policy documents in the European Union and in the United States that provide an ethical analysis of embryonic stem cell research. Sanctity of life and the status of the human embryo seem to be the most important issues in the American ethical assessment while the European reports present human dignity as the most fundamental ethical principle, and as a solution for ethical problems in stem cell research. In his contribution, *Maurizio Salvi*, the Head of the Secretariat for the European Group on Ethics in Science and New Technologies (EGE) discuss the ethical aspects and concerns that EGE considered in formulating its opinion on human embryonic stem cell (hESC) research. EGE, an advisory body of experts reporting to the European Commission, has been instrumental in developing European policies and research protocols in this field. Nevertheless, due to the lack of consensus among the European Union member states in interpreting the ethical implications of hESC research, scientific cooperation within the Seventh European Framework Program (FP7) has been so far hindered in this area.

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Ten years have passed since the reports on the birth of the first cloned mammal were published. This time has allowed scientists and politicians, bioethicists and legal experts to distance themselves from the legal norms prohibiting "all forms of human cloning", hastily adopted after the birth of Dolly the sheep. The position on the other extreme, which was initially overly optimistic about the benefits of stem cell research and fully endorsed the principle of freedom of scientific research, has also been reconsidered.

Regenerative medicine, the copying and substituting of human cells, is a permanently changing field of biotechnology. Using our own cells for therapeutic purposes changed the very concept of medicine. Hybrid embryos, chimeras and induced pluripotent stem cells further shift the debate from the problems of dignity and human substitutability to the biological versus social concept of the human being. The legal and political attitudes towards embryonic stem cell research seem to be more favourable than even two years ago – especially due to the recent changes in the position of the United States on the research use of embryonic stem cells, introduced by the Obama administration.[29]

Even in countries where one can observe a strong protection of potential life (in the context of abortion, for instance) embryonic stem cell research may be approved. An eminent example is the decision made in 2008 by the Brazilian Supreme Court to

[29] The National Institute of Health, a U.S. research agency, awarded USD 88 million of its USD 938 million stem-cell budget for human embryonic research in 2008. The money was limited to scientists who worked from about 20 lines of stem cells. Today's guidelines allow scientists working with embryonic stem cells to gain a share of the agency's USD 10 billion from the economic stimulus bill.

uphold the law that allowed the research use of embryos created during *in vitro* fertilization procedures that have been frozen for at least three years. Attorney General Claudio Fontelles challenged the law, saying it violates the right to life in the country's constitution. However, six of the high court's eleven justices upheld the law – indicating that new scientific and technological advances keep forcing us ethicists and legal scholars to constantly reconsider the ethical and legal, social and cultural implications of stem cell research and therapeutic cloning.

The field is growing incessantly; therefore we, at the Center for Ethics and Law in Biomedicine, could not have the ambition to address all major ethical and legal issues related to human cloning and embryonic stem cell research. Nevertheless, we believe that the chapters in this book will contribute valuable insights and new arguments to the ongoing ethical debates on regenerative medicine.

Acknowledgements: The production of this book was supported by the European Commission financed 7th Framework Project No: FP7-SSH-2007-1 on *Regenerative Medicine in Europe: Emerging Needs and Challenges* (Acronym: RemediE). I am very grateful for the help of the researchers at the CEU Center for Ethics and Law in Biomedicine (CELAB), especially to Enikő Demény and Petra Bárd who provided useful comments to the authors for improving the original version of their papers. And, as usual, I thank Miklós Vörös for his contributions to this book, without which the publication of *Perfect Copy? Law and Ethics of Reproductive Medicine* would not have been possible.

Nuclear Transfer Cloning: State of the Art

András Dinnyés

1. Overview of Nuclear Transfer Technology

Nuclear transfer (NT), also called 'nuclear replacement' or 'nuclear transplantation', is the method of choice for animal cloning. NT is a complex technique, which involves the removal/destruction of the nuclear DNA from an oocyte or zygote (enucleation), and replacing it with nuclear material from an embryo, stem- or somatic cell. The newly introduced DNA interacts with the recipient cytoplasmic environment, and following complex changes it will develop into embryos and in some cases into adult fertile animals.

Cloning is a natural process in many plants and simple organisms to reproduce asexually. However, initial cloning experiments were aimed to understand the differentiation process of the genetic material during development. The first experiments in the 1930's by Spemann[1] on salamanders revealed many basic mechanisms which are similar in mammals. In the 1950's and 1960's, with two frog species, it was shown[2,3,4] that embryonic cell nuclei transplanted into enucleated eggs reacquire a totipotent status and can develop into normal adults. Experiments using differentiated cells from adults were less successful, and only supported development to the swimming tadpole stage. Nevertheless, these studies proved that the donor cells retained all genetic information to form all the cell types in a tadpole, demonstrating that the genome is entirely preserved throughout cell differentiation and growth. Studies in amphibians then mammals[5] revealed that the potential of the nucleus to direct embryonic development decreases progressively with the developmental stage of the donor cell.

In mammals, the first experiments in the 1980's using embryo-derived blastomeres and sophisticated micromanipulation systems, resulted in the birth of numerous animals[6]. Due to the results in amphibians, researchers were initially discouraged to use

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