Foreword

In 1997, Ian Wilmut and colleagues from the Roslin Institute in Scotland published an article in *Nature* announcing the birth of Dolly the sheep, the first mammal to be cloned from an adult somatic cell.[1] The paper immediately made headlines around the world and raised serious concerns among ethicists and policymakers about the nightmarish prospect that the same procedure could be soon used to create genetically (and physically) identical human beings. In response to those concerns, intergovernmental organizations such as the United Nations, UNESCO, and the Council of Europe adopted policies to prevent that prospect from becoming a reality. Simultaneously, several countries did the same at the domestic level. But ethicists and legal scholars still had to face difficult theoretical questions: Do we have a right to the uniqueness of our genetic information? Are we entitled to predetermine the genetic makeup of our children? What value should we attach to sexual reproduction, that is, to the natural process by which every human being is conceived through the unique combination of genetic material from two different individuals? Does the present generation have a duty to preserve the integrity and identity of humankind?[2]

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[1] Ian Wilmut, et al., "Viable Offspring Derived from Fetal and Adult Mammalian Cells," *Nature* 385, no. 6619 (1997): 810-813.

[2] In the early 2000s, I had the opportunity to discuss some of those questions. See "Réflexions sur le clonage humain dans une perspective éthico-juridique et de droit comparé," *Les Cahiers de droit* 43, no. 1 (2001): 129:145, https://www.erudit.org/fr/revues/cd1/2001-v42-n1-cd3825/043632ar.pdf; "Biomedicine and International Human Rights Law: In Search of a Global Consensus," *Bulletin of the World Health Organization* 80, no. 12 (2002): 959-963, https://apps.who.int/iris/handle/10665/268678.

This book brings attention back to those difficult questions relating to cloning that have been to some extent forgotten in recent literature. While this foreword will not delve into all the nuanced arguments presented in the book, it will briefly touch on two main objections to human reproductive cloning: uniqueness and dignity. Through examination of both arguments, Protopapadakis ultimately concludes that they "do not suffice to convince us that cloning should not be considered a morally legitimate reproductive option."

I do not share this skeptical conclusion. The uniqueness of every human individual is closely linked to the very notion of "person." Throughout history, being a "person" has meant being a unique entity (a human individual) that has inherent value and cannot be reduced to a mere object. As Kant put it, a "person" cannot be replaced by something else as its equivalent precisely because he or she possesses "dignity" and not a "price."[3] It is true that the cloned individual would be a truly distinct person from his or her "model" (the cell donor) and from other "copies" that could have been produced from that same DNA. In other words, each clone would possess his or her own dignity, just like any other human being. However, the circumstance of being physically identical to other people would very likely pose a significant risk for his or her psychological identity; it will also be at odds with the legitimate interest of other individuals and society at large in being able to distinguish who is who. Our physical appearance, particularly our face, is not a minor or insignificant element of our personality. In fact, it strengthens our self-awareness and sense of self, as our body is the most direct and visible manifestation of our uniqueness.

[3] Immanuel Kant, *Grundlegung zur Metaphysik der Sitten,* in *Kant Werke,* vol. IV (Wiesbaden: Insel Verlag, 1956), 68.

There is almost no need to mention that the natural occurrence of monozygotic twins does not provide per se a justification for reproductive cloning. Not only because there is a fundamental difference between a *fact of nature*, for which nobody is responsible if it results in any harm, and a *human action*, which always is a source of responsibility, but because the mere fact that a certain phenomenon happens in nature does not necessarily authorize us to cause it *intentionally.* An earthquake that causes thousands of deaths is a perfectly natural phenomenon, and no one would deduce from it that we have the right to trigger the same dramatic result in order, for instance, to test the efficacy of a new weapon of mass destruction...[4]

Regarding human dignity, it is worth noting that this notion is often cited as the primary objection to reproductive cloning. This position is reflected in numerous international and domestic documents that prohibit this practice. It seems that we all share an underlying sense that creating genetically identical individuals is fundamentally problematic. Although it may be difficult to articulate precisely why, we intuitively recognize that reproductive cloning undermines a key aspect of human identity: our uniqueness and the inherent value of each of us.

Looking back on history, we may observe that the concept of dignity was traditionally used in bioethical discussions to highlight the intrinsic value of every individual (for instance, of participants in medical research). However, in the late 1990s,

[4] Additionally, monozygotic twins are an extremely rare occurrence, with only about 3 in 1,000 births. However, in reproductive cloning, there is no limit to the number of genetic "copies" that can be made of an individual, potentially resulting in dozens, hundreds, or thousands of clones. This would exponentially increase the risk of individuals having a diluted sense of identity.

human dignity began to be utilized to articulate disquiet about biotechnological developments, such as reproductive cloning and germline alteration, that may negatively impact *humanity as a whole*. In this more recent context, what is at stake is not so much the dignity of existing *individuals*, but the value we attach to the identity and integrity of the human species as such, that is, the *dignity of humankind*. It is important to mention that a purely human rights approach is powerless to face these new challenges because human rights are, by definition, only enjoyed by *existing* individuals, not by future people. This is why the well-intentioned claims often made that people have a "right not to be conceived as a genetic copy of another person" or a "right to inherit non-manipulated genetic information" are conceptually flawed.

The point I want to make is that the instruments dealing with bioethics that have been adopted since the end of the 1990s directly appeal to *human dignity*, and not to human rights, to ban human reproductive cloning and germline gene editing.[5] Three examples illustrate this trend: the UNESCO Universal Declaration on the Human Genome and Human Rights of 1997, which emphasizes the need to preserve the human genome as a "heritage of humanity" (Article 1), and expressly labels human reproductive cloning as "contrary to human dignity" (Article 11); the UN Declaration on Human Cloning of 2005, which calls on Member States "to prohibit all forms of human cloning inasmuch as they are incompatible with human dignity and the protection of human life" (Paragraph d); and the 1998 Additional Protocol to the Council of Europe Convention on Biomedicine and Human

[5] Roberto Andorno, "Human Dignity and Human Rights," in *Handbook of Global Bioethics,* eds. Henk ten Have, and Bert Gordijn, 45-57 (Dordrecht: Springer, 2014).

Rights, which prohibits human reproductive cloning on the grounds that it is "contrary to human dignity" (Preamble).

In conclusion, although I do not agree with all of Protopapadakis' arguments, I find his book to be a stimulating and thought-provoking read. It rekindles a vital discussion that has been largely overlooked by bioethicists over the past two decades or so. What is more, by thoroughly examining the objections raised against human reproductive cloning, the volume demonstrates that the underlying philosophical concerns are far more intricate than they initially appear.

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1. Seeking Wisdom in the Definition of the Terms

The phrase "the beginning of wisdom is the definition of terms" is usually attributed to Socrates, but it seems that it was probably the Cynic philosopher Antisthenes who first introduced an aphorism very similar to this one.[1] The question of the origins of the aphorism, however, is likely to be of interest only to scholars: The view that before any debate the terms should be defined in advance as fully as possible, "as in the measuring of corn we place first the examination of the measure,"[2] as Epictetus puts it, runs through all classical and Hellenistic philosophical thought, as is evident in Plato's dialogue *Cratylus*.

In the case of this book, an exhaustive definition of the key concepts that make up the theme of the book, namely human reproductive cloning, uniqueness, and dignity, would be impossible for several reasons: First, I am not a geneticist or biologist, so it would be very risky to seek a concise definition of human cloning. Therefore, in what follows, I will only attempt to convey to the reader what I understand human cloning to be after reviewing the relevant literature. Second, both the concept of uniqueness and that of dignity are extremely challenging, rich, and ambiguous. It takes more than a few pages to even begin to outline either concept. In fact, much

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[1] Antisthenis, *Fragmenta*, ed. Fernanda Decleva Caizzi (Milano, and Varese: Instituto Editoriale Cisalpino, 1965), D38: "The beginning of education is the definition of terms." The fragment is mentioned in Epictetus' *Discourses* – see next note.

[2] Epictetus, *Discourses of Epictetus*, trans. George Long (New York: D. Appleton and Co., 1904), Book I, XVII.

ink has been spent over the centuries trying to understand these concepts, so far without much success. In view of this, I had no choice but to propose the approach or approaches that I believe would be more fruitful for discussing the subject of this book, human reproductive cloning.

I. Cloning: What, how, why, and why not

It is often said that art copies nature; well, science also does so, and cloning is an iconic case of copying nature. Even first-year biology students are aware of the fact that with regard to the plant kingdom the existence of genetically identical organisms is a common phenomenon – so common that we do not even use the term 'clones,' but 'varieties' instead. When it comes to animal species, the presence of identical copies is much rarer. In several cases, however, such as in the case of single-celled protozoa like amoebae or bacteria, for example, reproduction takes place by means of binary fission, a process that produces two individuals with identical genomes,[3] a process that could accurately be described as cloning.[4] Some invertebrates also have the ability to regenerate fully as complete organisms from a small original part of theirs. Vertebrates lack this ability, but to some extent some of them can regenerate tissues, limbs, and organs.[5] It is statistically rare, but it is still a probability in

[3] See James Young Simpson, "The Relation of Binary Fission to Variation," *Biometrika* 1, no. 4 (1902): 402; also, Herbert Spencer Jennings, "Heredity, Variation and Evolution in Protozoa II. Heredity and Variation of Size and Form in Paramecium, with Studies of Growth, Environmental Action and Selection," *Proceedings of the American Philosophical Society* 47, no. 190 (1908): 393-546.

[4] David N. Wells, "Animal Cloning: Problems and Prospects," *Scientific and Technical Review of the Office International des Epizooties* 24, no. 1 (2005): 251.

[5] National Bioethics Advisory Commission, *Cloning Human Beings: Report*

the case of higher mammals that the division of a fertilized egg would result to two identical individuals, each one having the same genotype and phenotype as the other: This is the case of homozygous twins.[6]

Although to a large extent replication is a natural process that facilitates reproduction on a species level on the one hand, and also regeneration on individual level on the other, when it comes to human reproductive cloning, as it is always the case when natural *randomness* (or, necessity) is attempted to be artificially imitated and applied, an abundance of serious ethical questions and dilemmas arise, questions and dilemmas that fuel one among the most heated ethical debates of our times, the one on human reproductive cloning.

Cloning, though, is neither primarily, nor mainly, aimed at the replication of human individuals; as a matter of fact, human reproductive cloning is but a small cluster of a much broader scientific field, ranging from single-cell replication to the creation of identical organisms, and, as far as the latter is concerned, not always aiming to reproduction. As a generic procedure cloning is defined as the process of artificially (that is, under laboratory conditions) generating an exact (identical) genetic copy (called the *clone*) of any kind of biological material (called the *prototype*), be it a piece of DNA, a molecule, an individual cell, a plant, an animal, or a full human being. At the same time, the term also designates the scientific

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and Recommendations (Rockville, MD, 1997), 14.

[6] Mario F. Fraga, et al., "Epigenetic Differences Arise During the Lifetime of Monozygotic Twins," *Proceedings of the National Academy of Sciences* 102, no. 30 (2005): 10604. More recent research, however, questions the genotypic identity of homozygous twins; see Carl E. G. Bruder, et al., "Phenotypically Concordant and Discordant Monozygotic Twins Display Different DNA Copy-Number-Variation Profiles," *The American Journal of Human Genetics* 82, no. 3 (2008): 768ff.

research field that investigates and applies particular technologies, and nowadays constitutes an important subfield of experimental biology.[7]

a. From a frog to a sheep

In mammals, including humans, the method that has proved most successful so far is somatic cell nuclear transfer, and it has been the advances in this procedure that have brought the possibility of asexual reproduction in humans within reach: And this, even if it remains for the moment only a prospect, is definitely the culmination of a relatively short but rather glorious scientific journey. The description that follows provides a good overview of the potential, but also the limitations of cloning via somatic cell nuclear transfer:

> Cloning is achieved by somatic cell nuclear transfer (SCNT), in which chromosomes are first removed from an egg to create an enucleated egg. The chromosomes are then replaced with a nucleus derived from a somatic cell of the individual or embryo to be cloned.[8] Factors in the cytoplasm of the enucleated oocyte cause "reprogramming" or de-differentiation of the transferred nucleus so that it regains the full developmental potential of a zygotic (fertilized) nucleus, as occurs in the usual fusion of egg and

[7] National Bioethics Advisory Commission, *Cloning Human Beings: Report and Recommendations of the National Bioethics Advisory Commission* (Rockville, MD, 1997), 13.

[8] As cited in Malby, see below. R. S. Prather, and N. L. First, "Cloning of Embryos," *Journal of Reproduction and Fertility Supplment* 40 (1990): 227-234.

> sperm.[9] However, the construct created by SCNT also contains small amounts of extra-nuclear DNA derived from the egg (mtDNA).[10] Strictly speaking, therefore, a cloned person would not be 100% genetically identical to the prototype, since they would not have the same mtDNA (unless the female donor were to clone herself and also use one of her own eggs).[11]

Nevertheless, somatic cell nuclear transfer, the best possibility available to us today to reproduce identical copies of humans asexually, did not appear out of nowhere. The relatively short history of cloning began in the late 19th century with a frog and culminated in the present day with a sheep.

In 1892 the German evolutionary biologist August Weismann published his work *Das Germplasm: Eine Theorie der Vererbung*,[12] which he dedicated to the memory of Charles Darwin. In it he articulated for the first time his *germ plasm theory*: He argued, in particular, that multicellular organisms are composed of *germ cells* (gametes, that is, eggs and sperm cells) on the one hand, cells that contain inherited genetic information, and *somatic cells* on the other, whose purpose is to form organs, bones and tissue, and perform somatic functions; he also realized that inheritance may take place only through

[9] As cited in Malby, see below. M. Munsie, C. O'brien, and P. Mountford, "Transgenic Strategy for Demonstrating Nuclear Reprogramming in the Mouse," *Cloning Stem Cells* 4, no. 2 (2002): 121-130.

[10] As cited in Malby, see below. M. J. Evans et al., "Mitochondrial DNA Genotypes in Nuclear Transfer- derived Cloned Sheep," *Nature Genetics* 23, no. 1 (1999): 90-93.

[11] Steven Malby, "Human Dignity and Human Reproductive Cloning," *Health and Human Rights* 6, no. 1 (2002): 105.

[12] August Weismann, *Das Germplasm: Eine Theorie der Vererbung* (Jena: Fischer, 1982).

germ cells, but not through somatic cells. And while the latter are subject to environmental or other influences during the organism's lifetime, germ cells remain unchanged and are passed on intact to the organism's offspring. Sperm cells divide to produce somatic cells, which, however, do not possess all the genetic material of the original cell, but only that which is necessary for them to perform specialized functions. In other words, pancreatic cells may be the outcome of several successive divisions of a single germ cell, but they lack a large part of the genetic information contained in the initial germ cell. The information contained in them cannot be passed on to the offspring of the organism, since the transfer of genetic features is only achieved through germ cells. Hence, contrary to what Lamarck had assumed,[13] Weismann maintained that acquired characteristics cannot be inherited.[14] Weismann's views found enormous support in the findings of Wilhelm Roux, a German zoologist experimental researcher who, after having used a red-hot needle to destroy one of the two blastomeres of the embryo of a frog belonging to the species *Rana fusca*, observed that the remaining cell developed into an incomplete embryo; to him this was a proof that, already at the stage of the initial division, the original cell had lost half of the complete genetic information it originally contained.[15]

[13] Jean-Baptiste Lamarck maintains that acquired characteristics can be transmitted to the offspring of an organism through propagation; see among others Richard W. Burkhardt, Jr., "Lamarck, Evolution, and the Inheritance of Acquired Characters," *Genetics* 194, no. 4 (2013): 793-805.

[14] See August Weismann, *The Germ-Plasm: A Theory of Heredity*, trans. W. Newton Parker, and Harriet Rönnfeldt (New York: Charles Scribner's Sons, 1898; reprinted by Nabu Press, 2010), especially 450ff.

[15] The experiment and Roux's findings were published in 1988 as "Über die künstliche Hervorbringung halber Embryonen durch Zerstörung einer der beiden ersten Furchungszellen, sowie über die Nachtentwicklung (Postgeneration) der fehltenden Körperhälfte," *Virchows Archive für*