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The Ethics of Cellular Reprogramming

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Abstract

Louise Brown's birth in 1978 heralded a new era not just in reproductive technology, but in the relationship between science, cells, and society. For the first time, human embryos could be created, selected, studied, manipulated, frozen, altered, or destroyed, outside the human body. But with this possibility came a plethora of ethical questions. Is it acceptable to destroy a human embryo for the purpose of research? Or to create an embryo with the specific purpose of destroying it for research? In an attempt to construct ethical and legal frameworks for the new era of cellular reprogramming, legislators and ethicists have tried to distinguish between different kinds of biological entity. We treat cells differently depending on whether they are human or animal, somatic cells or gametes, and on whether they are embryos or not. But this approach to the ethics of cellular reprogramming is doomed to failure for the simple reason that cellular reprogramming in itself destroys the distinctions that the law requires to function. In this article, we explore the historical trajectory of cellular reprogramming and its relationship with ethics and society. We suggest that the early hype of embryo research has not obviously fulfilled expectations, but since new avenues of research are continuously opening, it is hard to say definitely that these promises have been broken. We explore the forthcoming challenges posed by the creation of DNA from scratch in the laboratory, and the implications of this for understandings of identity, privacy, and reproduction. We conclude that while ethics used to seek answers in biological facts, this is no longer possible, and a new approach is required.

Keywords: ethics, stem cells, embryo, IVF, cloning

Historical Background

Louise Brown's birth in 1978 heralded a new era not just in reproductive technology, but in the relationship between science, cells and society. For the first time, human embryos could be created, selected, studied, manipulated, frozen, altered, or destroyed, outside the human body. But with this possibility came a plethora of ethical questions. Is it acceptable to destroy a human embryo for the purpose of research? Or to *create* an embryo with the specific purpose of destroying it for research? For many scientists, the answer was clearly yes. The benefits to be gained from stem cells were immeasurable; the ability to create any cell from a human body would revolutionize medicine—at least in theory. It would mean that heart, lung, brain, or blood cells could be generated from embryonic stem cells (Paul et al., 2002).

In the United Kingdom, the question of whether scientists should be able to pursue these avenues was debated in parliament and in February 1985, the Unborn Children (Protection) Bill ''confirmed the worst fears of the scientific community'' (Mulkay, 1997). The vote against embryo research was 238–66. In response to this, scientists embarked on a quest to convince the public of the *need* for embryo research. As Mulkay puts it, it became clear that ''research has to be justified to the satisfaction of the lay community and its parliamentary representatives'' (Mulkay, 1997, p. 26).

A schism opened up between opponents of embryo research and those who supported it. This was mirrored by a

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broader social and political divide, whereby the new Labour Government explicitly aligned itself with scientific progress (Bruce, 2002). Ultimately, the scientific community won the battle. The law stipulates that human embryos used in research have a special status. They should not be treated frivolously. The law, however, is premised on a fact that in itself comes into question once the doors to cellular reprogramming are opened: what *is* a cell, an embryo, or a gamete? What does it mean to say that a cell or embryo is human?

Ethics and Embryonic Stem Cell Research

Embryo research no longer generates as much antipathy as it used to. As with *in vitro* fertilization (IVF), people became accustomed to the unfamiliar. The minority who continue to oppose both IVF and embryo research are often those with strong religious affiliations (Crockin, 2005). While this may appear reassuring, it raises a troubling question for those interested in ethics, science, and society. As Lee and Morgan observe, social mores change constantly (Lee and Morgan, 2001). Are we to assume there is no further basis for moral judgment than what is currently accepted?

The question of whether morality is socially determined is an ongoing matter of philosophical debate, and we do not attempt to answer it here. Rather, we outline the various ethical challenges raised by aspects of scientific research, and the ways in which different moral approaches suggest different answers.

In the context of embryo research, the following ethical issues arise:

- the moral status of the human embryo
- the benefits to be gained from experimenting on embryos
- the effects on society of using embryos as research objects

Opponents of embryo research may regard human embryos as having the same moral status as any other human adult or child, right from the moment of conception. Another way of thinking about this is in terms of dignity and rights. We take it that as humans, we have certain rights, and that this in turn imposes obligations on others. But while it is easy to make sense of these concepts in relation to the human beings we encounter in our ever day lives, it is not obvious how or whether they should apply to embryos and fetuses.

Those who support embryo research often claim that it is misguided to suppose that a mere cell (the fertilized egg) can have the same moral significance as a fully grown human being with the power to reason, to suffer, and to communicate. It is undeniable that a newly fertilized egg lacks the power to reason and communicate. However, it is questionable whether we can thereby dismiss it as a mere cell. Clearly, it is a very special cell—one that has the potential to develop into a new human being.

When it comes to the question of suffering, few people would claim that a newly fertilized cell, or an eight-cell blastocyst, has the ability to feel pain. Yet at some point along the developmental trajectory, these capacities must develop. As far as we know, biological organisms cannot feel pain unless they have a nervous system. The embryo's spinal column begins to develop at around 14 days after conception. Accordingly, the law takes a somewhat precautionary approach, in ensuring that all embryos used in research must be destroyed by the 14th day.

The idea that it is preferable to destroy an embryo rather than keep it alive is, of course, in itself morally problematic. For opponents of embryo research, it is a compromise that makes little sense, but the legislators needed a pragmatic solution that would permit embryo research within certain parameters, rather than a morally or philosophically robust account of the moral status of an embryo. This wish to facilitate embryo research was based on a conviction that there were significant benefits to be gained from such research.

As noted above, when parliamentarians and scientists began lobbying in favor of embryonic stem cell research, extravagant claims were made about the medical, technological, and economic benefits of such research. It was argued that scientific freedom and progress should be restricted only reluctantly, and in the face of compelling evidence as to the negative consequences of failure to do so (Wilsdon et al., 2005). A new mood of aggressive political optimism with regard to scientific advances emerged (Parliamentary Office of Science and Technology, 2002). Brain, heart, and lung cells could be generated for those suffering from cancer. Organs could be grown in laboratories for transplant. Those who opposed embryo research were asked how they could possibly justify placing the protection of embryos above the needs of patients who were suffering and dying of diseases that could be cured.

Somatic Cell Nuclear Transfer

The news that a sheep had been successfully cloned generated further shockwaves. Cloning conjured images of dystopian science fiction. Suddenly, any cell had the potential to become a new individual. A flurry of hasty legislation and declarations emerged, affirming that reproductive cloning must never be undertaken in human beings. Human reproductive cloning violates human dignity; it is not reproduction, but replication, asserted the WHO (World Health Organisation, 1998). The influential bioethicist John Harris disagreed, arguing that reproductive cloning might offer a means of fulfilling people's reproductive autonomy (Harris, 2004). For Harris and others, the issue is not one of emotion, revulsion, or human dignity, but whether possibilities such as cloning would cause harm to the resulting offspring. If not, Harris claimed, there could be no reason to forbid cloning.

Leon Kass suggested that cloned children would be isolated beings of the world, lacking the biological connections that tie the rest of us together.

> ''Every one of us is at once equally human, equally enmeshed in a particular familial nexus of origin, and equally individuated in our trajectory from birth to death'' (Kass, 1998, p. 25).

Kass further argues that the intuitive revulsion people feel about deviations from the natural should be recognized as a serious indication of moral wrongness (Kass, 1998). It is clear that the term ''unnatural'' is often emotionally loaded and connected with negative moral implications. In everyday language: natural is authentic, artificial and synthetic are not (Loike, 2014). However, the form of argument adopted by Kass has been criticized by those who regard it as

excessively emotive or irrational (Nuffield Council on Bioethics, 1999; Smajdor, 2015).

Those who favored a more utilitarian line of reasoning were particularly excited by the idea that the new cloning breakthrough would enable scientists not only to develop heart, lung, or brain cells on demand, but would facilitate the creation of stem cells derived from embryos cloned from the potential recipient's somatic cells. These stem cells would, of course, be an exact match for the recipient (Kfoury, 2007). In this way, the risks of rejection would be avoided. Accordingly, the arguments based on the potential benefits of embryonic stem cell research became still more weighty in their promise for curing disease and suffering.

The distinction between ''reproductive'' and ''therapeutic'' cloning came into being. Therapeutic cloning was regarded by many as being acceptable because (1) it met a verifiable medical need (as opposed to a mere desire to replicate oneself), (2) because the cloned embryo would never be implanted into a uterus, or brought into existence, and (3) because the law provided a robust and reputable framework wherein this sensitive work could be undertaken.

Induced Pluripotent Stem Cells

As the science progressed, it became clear that cells could be ''programmed'' to behave like embryonic stem cells, without the need to create a human embryo first. These reprogrammed cells were termed ''induced pluripotent stem cells'' (iPSCs). Since embryos do not have to be destroyed for us to create pluripotent cells, this may seem like a win from all ethical perspectives. Yet the need for, and use of, human embryos has not disappeared with the emergence of iPSCs. Indeed, further challenges have evolved, in particular with the discovery that human embryos can in fact be cultivated *in vitro* for longer periods than initially envisaged.

When the law stipulated that embryos must be destroyed within 14 days, as noted above, the idea was that this would enable researchers to be confident that the organisms they were working with had no capacity for consciousness or sentience (Deech and Smajdor, 2007). But this moral precaution was in a sense not precautionary at all. It was not the 14-day rule that prevented scientists at the time from keeping embryos *in vitro* beyond this point. It was simply not possible for them to do so. Thus the law functioned as a symbol of society's moral concerns, rather than as an effective means of preventing certain actions that would otherwise have taken place.

More recent developments suggest that the previous limitations may no longer apply. The prospect of keeping embryos *in vitro* past 14 days is becoming technically feasible in a way that was not possible a few decades ago (Hyun et al., 2016). Accordingly, some have called for a review of the 14-day rule (Appleby and Bredenoord, 2018). Not because the moral issues have changed, but because scientists see new possibilities opening up. But some moral questions are still left unanswered. Have we seen the enormous benefits of embryo research that we were promised? Have we saved the sick and dying whose suffering formed the rhetorical impetus behind embryo research?

These questions are almost impossible to answer. The utilitarian arguments for embryo research were in some respects as vague as those that drew on concepts of dignity or moral worth: pictures of a bright future at some unspecified time point. Because of this vagueness, it is hard to say whether the results of embryo research fulfilled their early promise, and thus whether the utilitarian perspective was vindicated.

Biological Boundaries

With the ebb and flow of scientific discovery, it has become increasingly apparent that the distinctions that we rely on in our legal and ethical reasoning are not biologically fixed, but are open to change. The law treats human embryos very differently from other human cells and tissues. It distinguishes between animals and humans, and it distinguishes between gametes and somatic cells, between embryos created for reproduction, and those created for research. But with cellular reprogramming, as we have seen, a somatic cell may become an embryo; a skin cell may become a gamete (Newson and Smajdor, 2005; Testa and Harris, 2005). Animal DNA may be mixed with human. In this environment, the ethical challenges are immense. The question of how we should treat a human being, an embryo, or a gamete becomes secondary to the question of how we define these entities. What should be apparent, as a result of this, is that biology itself will not give us answers to moral questions. Instead, the moral sphere has bled into what used to be regarded as a purely scientific domain. The question of what is a human embryo is one of philosophical and ethical deliberation and negotiation.

Advances in DNA Synthesis from Yeast to Human Genomes?

In the first part of this article, we adopted a primarily retrospective approach to the exploration of moral and legal responses to successive developments in cellular reprogramming. In this second part, we turn our attention to new possibilities on the horizon, focusing on the creation of DNA strands *in vitro*.

The first living organism to have its genome fully sequenced was the bacterium *Haemophilus influenza* in 1995 (Fleischmann et al., 1995), the first draft of the human genome was later published in 2001 (International Human Genome Sequencing Consortium, 2001; Venter et al., 2001). Similarly, the CRISPR genome-editing technique was first tested in bacteria in 2012 (Jinek et al., 2012) before eventually progressing to the first human clinical trial launched in 2016 (Lu et al., 2020). Following this sequence, recent achievements in the field of DNA synthesis in yeast and bacteria suggest that it may merely be a matter of time before we are able to build human DNA sequences from scratch in the laboratory.

Artificial gene synthesis involves the concatenation of nucleotides in whatever order the creator or designer chooses, giving rise to synthetic DNA molecules (synDNA). In 2007, a research group succeeded in constructing and transplanting an entire artificial genome (Lartigue et al., 2007). Specifically, they replaced the complete genome of *Mycoplasma capricolum* with a newly synthesized genome of *Mycoplasma mycoides*. The modified bacteria exhibited the behavior anticipated for *M. mycoides*, confirming that the new genome had successfully produced the expected phenotype.

In 2016, a comprehensive redesign of the *M. mycoides* genome was undertaken with the purpose of eliminating all

genes deemed unnecessary for the bacteria's survival (Hutchison et al., 2016). This was a significant milestone, involving the synthesis of the first DNA sequence entirely redesigned using computer-based methods. The resulting bacteria were able to proliferate successfully.

In 2014, another group achieved the synthesis of a chromosome of the yeast *Saccharomyces cerevisiae* (Annaluru et al., 2014), a eukaryotic organism. This and the achievements described above all involved the concatenation of relatively short genomes. While the creation of longer DNA strands, including entire human genomes, remains a feasible yet daunting prospect, the ability to create whole or partial artificial human genomes has profound ethical implications.

Privacy, Identity, and synDNA

It is widely accepted that we have a right of privacy in regard to our genes. This imposes constraints on others in terms of who can access our genetic information and how such information can be used. This element of privacy aligns with the notion that genes are to some extent inaccessible. However, with the possibility of creating human genes or genomes from synDNA, numerous questions arise concerning the relationship between genes and privacy. How is our privacy affected when a scientist recreates an individual's gene in the laboratory? In an era where genetic determinism and reductionism have been discredited, arguments surrounding genetic privacy lose some of their persuasiveness. Consequently, the emergence of synDNA not only calls for a careful examination to establish a normative framework to distinguish between permissible and nonpermissible practices but also challenges our current conceptions of privacy in the genomic era.

A similar issue arises concerning the concept of identity. The prevailing assumption holds that genes play a crucial role in shaping our identity, influencing various aspects of life, including privacy regulations, health care practices, reproduction, and family relationships. Consequently, the question of what constitutes ''my'' genes becomes central, especially if ''my'' genes are being (re)created by a third party, perhaps without my knowledge or consent. In such a scenario, the prospect of gene replication could raise ethical concerns. However, upon closer examination, the idea that any specific gene plays a significant role in shaping our identity is hard to sustain. Genes, in themselves, have rather mundane biological functions. Each gene serves as a minuscule molecular machine responsible for producing a specific protein.

Even if we recognize that it is the configuration of genes, rather than any specific gene, that holds significance for identity, we still encounter important questions regarding what happens when these patterns are fragmented or disassembled. Unlike bodily tissues, genes seem to be uniquely linked to identity. People may donate blood or lose limbs without feeling that it jeopardizes their core identity. Perhaps, in the light of synDNA, we should reconsider the relationship between genes, identity, and privacy.

Challenging Parental Status

Genetic transmission is regarded as one of the most pivotal aspects of reproduction. However, the advent of synDNA technology poses new questions about parental control and autonomy. The possibility of scientists creating and inserting personalized genes into cells challenges our understanding of what reproduction is. While synDNA offers the potential for prospective parents to avoid passing on specific genes or selectively choose genes for their offspring, it challenges the traditional notion of reproduction as a matter of chance. Additionally, the idea of designing aspects of synDNA rather than relying on genes from prospective parents raises fundamental questions about the extent of genetic alteration that would still be consistent with considering oneself as the parent of the resulting offspring. As we delve deeper into the realm of synDNA, it is clear that the challenges of the past are by no means resolved. Further complexities emerge with each subsequent development.

Conclusion

Reprogrammed cells and constructed DNA sequences can be viewed as partly artefactual. They are closer to being objects than ''ordinary'' cells or DNA strands. This means that our relationship with them is also different, in ways that may be morally significant. Hannah Landecker puts this nicely when she suggests that bioethicists missed the point about the cloning of Dolly the sheep: the real revolution was not the replication of a genome, but that something had happened which ''alters what it is to be made of cellular biological matter'' (Landecker, 2007, p. 225). We have the power to direct and alter biological processes, or again in Landecker's words, we have gained control of ''the plasticity of living matter'' (Landecker, 2007, p. 225). This gives us new moral powers and responsibilities. As Habermas notes, when we take control over biological processes, ''we have to answer'' for them (Habermas, 2003). The trajectory of cellular reprogramming shows us that relying on absolute biological boundaries in our moral concepts and reasoning is misguided. Yet we tend to continue to seek answers that are precise definitions and distinctions. As the prospect of synDNA becomes a reality, we have an opportunity to revisit and critically evaluate the moral concepts and assumptions of the past. In this way, we may face the future better equipped to deal with its inevitable challenges and complexities.

Authors' Contributions

A.S. wrote the first half. A.V. wrote the second half. A.S. edited the full draft.

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