Reprogramming Somatic Cell Differentiation and the Hayflick Limit: Contrasting Two Modern Molecular Bioengineering Aims and Their Impact on the Future of Mankind

E. SCOTT SILLS,¹ TAKUMI TAKEUCHI,² ZEV ROSENWAKS,² and GIANPIERO D. PALERMO^{2,3}

Submitted: April 19, 2001

Accepted: April 25, 2001

The molecular biology of human cloning and aging research depend on the closely related laboratory techniques supported by a thorough understanding of cell-signaling processes. Unfortunately, the link between these two research fields has received only marginal attention in the lay press. Cloning is possible when somatic cell differentiation is successfully reprogrammed, and clinical control of cellular senescence depends on a proper reconfiguration of the predetermined number of divisions permitted during the cell life-cycle (the so-called "Hayflick Limit"). In this paper, we discuss these two concepts and compare the impact likely to be associated with bioengineering studies that facilitate both human cloning and longevity therapy.

KEY WORDS: cloning; ethics; research; relativism.

"Fundamental progress has to do with the reinterpretation of basic ideas."

Alfred North Whitehead
(1861–1947)

CLONING AND AGING: EMERGING PATHS, DIFFERENT DESTINATIONS

Two irreducible realities of the human experience are the concept of a unique, personal existence and our

awareness of a limited lifespan. That plausible interventions to change these processes could even be proposed is a tribute to the rapidly growing information derived from multidisciplinary work in human genetics, biogerontology, oncology, and reproductive biology. Over the past several decades, science has gradually deconstructed the philosophical concepts of human cloning and longevity by offering embryo splitting, human nuclear somatic cell transfer (NSCT), and gene therapy, respectively, as means to bring them within reach. While cloning has received much publicity, studies of the genetically preordained physiologic allowance of cell divisions after which a cell must die (the so-called Hayflick Limit (1)) have regrettably passed nearly unnoticed. While these processes are not refined for clinical use now, both will be closer to mainstream medical practice within 50 years if the current pace of discovery is maintained. Since experimental regulation of cellular differentiation and aging depends on precise governance of cell synthesis signals, a considerable overlap in molecular technique will probably be required to alter either processes safely.

We consider the technical features of human aging and cloning research to be opposite sides of the same coin. Unfortunately the link between these research fields has received insufficient attention, resulting in a misunderstanding of the full scope and impact of experimental human molecular biology. Cloning has become merely the most proximate and tangible sensation from the spectacular world of medical breakthroughs. Since a sheep with enhanced longevity has not been experimentally developed (yet), the important work in human aging is correctly perceived

¹ Georgia Reproductive Specialists LLC, Atlanta, Georgia.

² Center for Reproductive Medicine and Infertility, Weill Medical College of Cornell University, The New York-Presbyterian Hospital, New York, New York.

³ To whom correspondence should be addressed at 505 E. 70th Street, HT-336, New York, New York 10021.

as more remote in terms of readiness to move into the clinical arena. However, since considerable resources continue to drive both fields of study, we may not need to wait long before either cloning or controlled cellular senescence is clinically available. Can the cloning controversy help prepare us for this next social debate? How will the utilization of human cloning services compare with the utilization of a human longevity therapy? In this essay, we contrast some ethical implications of sexual and asexual human reproduction strategies, as well as the prospect of delayed human aging in a philosophical framework. Given the apparently acceptable uncertainties of human sexual reproduction, the early alarms evoked by human reproductive cloning may be greater than circumstances warrant. Furthermore, if related molecular research on the genetics of cellular aging foreshadows a workable way to decelerate human aging, the present ethical exercise accompanying human cloning would be swiftly outranked.

LESSONS FROM THE PROGERIAS AND MONOZYGOTIC TWINS

The naturally occurring but exceedingly rare conditions believed to mimic accelerated human aging (collectively termed the “progerias”) gave early observers their first suspicion that aging in humans may not necessarily be time-dependent, just as monozygotic twins shattered the belief that everybody has to have a distinctly unique genetic array. What had stumped the experts until quite recently was how to solve the problem of somatic cell dedifferentiation (for cloning), or how to extend the preprogrammed number of cell divisions beyond which cellular death occurs (for aging) (1). As reproductive specialists, we are more familiar with the approaches used in mammalian cloning (discussed elsewhere in this issue), but developments in the field of biogerontology share some interesting features and also deserve an overview.

When confronted with damaged DNA, cells either initiate repair or undergo apoptosis. The checkpoint proteins p53 and ATM (ataxia telangiectasia/mutated), for example, appear to block DNA replication of damaged DNA until its repair has been effected. If such proteins are missing or defective, inappropriate cell growth or loss may result. Should DNA damage exceed the checkpoint mechanism and preclude repair, a degenerative physiologic state could occur. Like cloning research, current

studies of aging and cancer research have focused on this subcellular signaling, to better understand how such checkpoint proteins are activated and to elucidate how to “re-write the program” in the life and death cycle of human cells. Work in other species has suggested that cell lifetime might be constrained by some finite number of cellular divisions. If this “Hayflick Limit” could be substantially lengthened by enhanced telomerase activity or some other genetic modification for human cells, the significance of such a bioengineering feat would be difficult to estimate as the eventual consequences for humanity would be of near insuperable magnitude. We do not believe this would necessarily be the case with human reproductive cloning, especially when the risks associated with our current mode of reproduction are viewed dispassionately.

CONSIDERING THE ALTERNATIVE

Across all Earthly phyla the familiar procreative strategy that humans take for granted, sexual reproduction (via meiosis and gamete recombination), represents a distinct minority voice. Unlike humans, most organisms cataloged thus far do not reproduce according to this remarkably inefficient scheme. Indeed, our molecular ballet of reproduction comes at high cost, in evolutionary terms. Can we imagine that it might be any other way for us?

Consider for a moment the hypothetical position that *asexual* reproduction (a.k.a. “cloning”) has in fact been the routine mode of *H. sapiens* reproduction for millennia. In this frame, we are accustomed to cloning, all human babies come from cloning, cloning has worked just fine for as long as anyone can remember, and this is all we have ever known. Suddenly, a radical discovery is made. Preliminary research suggests that human babies might be made by something called sexual intercourse, although this could not immediately be confirmed by independent laboratories.

The announcement is first met by protests of disgust and repulsion. Our full institutional and academic apparatus soon is entrained on the possibilities of this discovery, and we immediately begin to collect an inventory of all possible social, ethical, and legal problems that might befall us if the technique of sexual intercourse became widely practiced. The issue is of tremendous significance, since human dignity is in the balance.

In this hypothetical scheme, an early and especially shrill argument against sexual reproduction would

center on its inherent waste, since when observed in several animal models, the process either didn't work at all or resulted in spontaneous abortion. After more deliberation, there is speculation that the human child conceived by sexual intercourse would be forced to divide its attention between *two* progenitors, a circumstance posed to bring about confusion and guilt. The undesirable impact this conflict would have on interpersonal development, socialization, and core identity would become the topic of much media play.

Ethics panels gain an additional insight: accidents might happen, for the two people responsible for the child might not consent fully to the conception. What new mechanism would need to be in place to resolve disputes of this kind? Cross-cultural critiques of sexual reproduction might hypothesize that a baby's two parents could even split up, a regrettable and destabilizing event decried by some as inhumane. The voice of medicine would urge characteristic caution, because there would also be biological risks associated with sexual reproduction—risks few of us would be prepared to take. For example, the potentially lethal prospect of sexually transmitted disease would now need to be considered. Furthermore, the configuration of the baby's genetic composition would be utterly random. Perhaps more consequentially, a child could inherit double copies of harmful recessive alleles, causing incalculable harm to the human genome. These last two objections would be sufficient grounds for some to call for an outright Federal ban on sexual intercourse research.

As Stone (2) has observed, in the real world, society has succeeded in meeting the challenges associated with each of these complex issues *reasonably* well. Indeed, our adaptation to the particular phenomenon of monozygotic twins (and other monozygous multiples) stands as nature's best lesson on how to regard the occurrence of these "natural human clones." Should the results from iatrogenic human cloning be judged any differently?

CONCLUSION

Both in technical and ethical terms, human reproductive cloning has been associated with the potential for significant harm from the outset. Although per-

haps less appreciated, this critique could also apply to research on cellular aging and death; yet there have been no calls to curtail work in this area. In cloning, early experiments in animal models have shown a proclivity for abnormal embryo and fetal development, a high miscarriage rate, and numerous congenital anomalies. Studies of the surviving mammalian clones suggest that a high frequency of macrosomia or premature aging conditions may be problematic, and several theoretical explanations have been advanced to explain these findings. The putative psychological implications of human cloning are equally complex and hotly contested. At the same time, biogerontology studies on apoptosis, human aging, and death have received a much cooler media welcome. As with cloning, the technology enabling enhanced longevity will likely become available first to the elite few with the power and means to use it, but with social, demographic, moral, and political ramifications far beyond those associated with human cloning. Have our social commentators decided to overlook this possibility, preferring instead to dwell on the more immediate but comparatively less substantial cloning issue?

The ethical implications of sexual and asexual human reproduction strategies, as well as the techniques to extend human lifespan, have been inadequately contrasted in a philosophical framework. Indeed, if related molecular research on the genetics of cellular senescence can yield feasible therapies to delay aging in coming decades, our present ethical exercise with human cloning will be easily bested by a medical achievement of truly epochal proportions.

If it is our ego that drives us to embrace human cloning, then it may be our fear that prompts the hopeful interest in longevity research. Could it be that the notion of postponing the sting of death is easier for us to accept than the possibility of seeing a genetic copy of ourselves? Perhaps not surprisingly, it will be the comprehension of human genetic processes that ultimately will potentiate both of these difficult choices.

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