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Human in vitro eugenics: close, yet far away

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The article on human in vitro eugenics by Sparrow is provocative and pertinent.[1] Nonetheless, practical limitations to the technique of creating human gametes from stem cells have not been considered. Those limitations are relevant as they lead to ethical complications of higher magnitude than those presented in the paper.

One practical limitation to the technique is that, no matter how a pluripotent cell is created, it is still a diploid cell. In order to make gametes out of such cells, they must be induced to undergo meiosis, which will turn them into haploid cells. Only haploid gametes could fuse to generate a true zygote. Mitosis is distinct from meiosis; in the former, segregation of DNA is equal throughout all cell generations, but this does not apply to the latter. In meiosis, heterozygous genes segregate differently to form different gametes. Moreover, numerous other processes become activated during meiosis in order to provide the individual with the largest possible array of genetically diverse gametes. Processes such as homologous recombination and crossing-over are quite frequent during meiosis, causing small pieces of DNA to be exchanged among chromosomes.[2] Mammalian spermatogenesis, for instance, is divided into three phases: first, primitive diploid germ cells undergo mitotic divisions to increase their numbers; next, they undergo meiosis to produce haploid spermatids; and, finally, they differentiate into true gametes through a number of cell modifications that turn them into fully mobile spermatozoa. In this last phase there are no further divisions, only differentiation.[3] Indeed, fully mature gametes are neither cultivable nor cloneable as they cannot undergo mitosis. It would therefore be virtually impossible to screen for a single gamete with the desired genetic trait without destroying it in the process, thus making it useless for any downstream protocol. This limitation would have to be overcome if the technique is to be used for genetic improvement.

Another important constraint of in vitro eugenics is that the shortening of generations—a possibility raised by the author as a way to study the presentation of genetic disorders—may have a significant impact on how a disease manifests itself. The author acknowledges that the impact of multiple gene interactions and the environmental role in the phenotype of an experimental subject may have been neglected in discussions prompted by in vitro eugenics. Nonetheless, a third important aspect may have gone unnoticed. Some diseases are not only a result of multiple gene interactions or of environmental pressure, but also a result of some types of cell and tissue interaction caused by biological ageing. As we age, genes are turned on and off, which leads to growth and maturation of the body. This is mostly achieved by the production of chemicals—mainly hormones—that work as a way of communication between cells. Many genetic disorders evolve only after a certain age when hormones and chemicals are produced and set in motion the physiological onsets that generate a disease condition. This goes beyond gene interaction within a single cell and is related to the complex interactions that take place within the organism as a whole. All this complex net of tissue-to-tissue cross-talking will simply not happen if generations are shortened down to the embryogenic level before the next generation starts from cells of the previous one. Thus, after something like 20 in vitro generations, will a disease manifest in the 21st subject as it would after 20 real generations? Or will it simply manifest in the second generation after the study began? In other words, can we really consider that there were 20 generations between the two terminal ones? Even in the microcosmos created by the multiple in vitro generations prospect, problems may arise from the fact that the next generation in line is derived from cells taken from a simple mass of embryo cells and not from a more developed organism. Again, taking the mammalian spermatogenesis as an example, it is agreed that the process of gamete-making is regulated by the information contained in the cell undergoing genesis and also by paracrine, juxtacrine and endocrine pathways.[3] This means that surrounding cells and tissues are essential for spermatogenesis, and these will simply not be there during the process of gamete derivation from pluripotent embryonic cells.

There is no doubt that the creation of gametes from somatic pluripotent cells and the possibility of multiple generation testing in a short time frame are potent tools to study genetic segregation throughout the generations. Patterns of how genes are segregated among gametes, how they would become imprinted on the population and many other interesting questions could be answered by multiple in vitro generation studies. In this context, would it be possible to study the behaviour of disease-related mutated genes along consecutive in vitro generations? It is tempting to speculate that the identification of patterns of dispersion of genetic disorders in vertical studies would be feasible. Still, the final phenotypic result of such studies would always have to rely on bringing an embryo to term at some point. Even then, there is always the risk that, while scientists focused their sights on a single gene or a limited group of genes, millions of other gene interactions may have happened. How that would affect the desired trait or the whole fitness of the subject is difficult, if not impossible, to foresee. It is relatively acceptable to experiment with this in laboratory mice or even in farm animals as a way to improve their genetic attributes. But the risks are far too great—and unknown—to pursue this in humans.

Practical limitations of the technique therefore lead to much bigger ethical conundrums than the ones pointed out by Sparrow. The technique would only achieve a level of desirable success and reliable data, according to scientific standards, if and when the human embryos produced are brought to term. The creation of mature humans past the embryonic stage following the presented technique seems to be far from being ethically and socially acceptable.

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Contributors BS came up with the idea of writing this commentary and, following discussions between all the authors, drew up a general sketch of what was to be written. FGdF was responsible for researching and writing the larger part of the text

regarding issues surrounding human spermatogenesis and epigenetics, and providing the references for the remarks on the subject. BS and DMR were responsible for drafting the (brief) ethical commentaries concerning the practical limitations of in vitro breeding of human gametes. NPC and DMR, under supervision by BS, were responsible for reporting and structuring the arguments and revising the language for the final draft. FGdF and BS are responsible for the overall content as guarantors.

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