IN VITRO EUGENICS

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ABSTRACT:

A series of recent scientific results suggest that, in the not-too-distant future, it will be possible to create viable human gametes from human stem cells. This paper discusses the potential of this technology to make possible what I call "*in vitro* eugenics": the deliberate breeding of human beings *in vitro* by fusing sperm and egg derived from different stem cell lines to create an embryo and then deriving new gametes from stem cells derived from that embryo. Repeated iterations of this process would allow scientists to proceed through multiple human generations in the lab. *In vitro* eugenics might be used to study the heredity of genetic disorders and to produce cell lines of a desired character for medical applications. More controversially, it might also function as a powerful technology of "human enhancement" by allowing researchers to use all the techniques of selective breeding to produce individuals with a desired genotype.

Keywords: Gametogenesis; Ethics; Stem Cells; Human Enhancement; Eugenics; Gametes.

IN VITRO EUGENICS

INTRODUCTION

A series of recent scientific results suggest that, in the not-too-distant future, it will be possible to create viable human gametes from human stem cells.[1-5][i] Should this turn out to be the case, it will dramatically expand the number and type of individuals—and combinations of individuals—for whom reproduction will be possible and will consequently require a concerted effort to extend and revise current accounts of the ethics of reproduction. Some of this intellectual work has already begun, with philosophers and bioethicists discussing the ethics of posthumous and same-sex genetic parenthood with renewed enthusiasm. However, the development of a technology of *in vitro* gametogenesis would also make possible other technological interventions into human reproduction, which as yet have barely been discussed at all. In particular, it might allow what I will call "*in vitro* eugenics": the deliberate breeding of human beings *in vitro* by fusing sperm and egg derived from different stem cells lines to create an embryo and then deriving new gametes from stem cells derived from that embryo, which in turn might be used in the creation of another embryo. Repeated iterations of this process would allow scientists to proceed through multiple human generations "in the lab".[ii] *In vitro* eugenics might be used to study the heredity of genetic

[i] Assessing what might become possible in the future using assisted reproductive technology is a daunting task given the pace at which biological science is progressing and the range of expertise – including, but not limited to, knowledge of reproductive biology, molecular biology, genetics, epigenetics, ethics, law, and politics – required. As someone whose disciplinary expertise lies in philosophy, I am especially fortunate to have been the beneficiary of the generosity of a number of scientists and other researchers who have provided comments and discussion on this manuscript. In particular, I would like to thank: Peter Temple-Smith at the Faculty of Medicine, Nursing and Health Sciences at Monash University; Shae-Lee Cox at the School of Biomedical Sciences at Monash University; Susan Hawes at the Centre for Human Bioethics at Monash University; Jeremy Brownlie at Griffith University; Jeffrey Craig, at the Murdoch Children's Research Institute; Justin St John and Patrick Western at the Centre for Reproduction and Development, Monash Institute of Medical Research; Giuseppe Testa at the Laboratory of Stem Cell Epigenetics, European Institute of Oncology; Debra Mathews at the Berman Institute of Bioethics, Johns Hopkins University; and Ian Kerridge, at the Centre for Values, Ethics and the Law in Medicine, University of Sydney. Responsibility for any errors remaining in the manuscript remains, of course, my own.

[ii] Mathews et al. note the potential of *in vitro* gametogenesis to facilitate the "practice of *in vitro* genetics" for research purposes, so that "scientists will be able to conduct multigenerational human genetic studies in a dish".[4] They also draw attention to the fact that *in vitro* gametogenesis may facilitate human enhancement by greatly increasing the power of PGD by removing current limits imposed by the small number of eggs salvaged in each cycle of IVF. Bourne, Douglas, and Savulescu investigate at length the power of *in vitro* gametogenesis to enhance the human genome and advocate its use to this end.[6] However, to my knowledge, the current paper is the first to explicitly discuss the possibility of the iterative use of this technology for reproductive purposes

disorders and to produce cell lines of a desired character for medical applications. More controversially, it might also function as a powerful technology of "human enhancement" by allowing researchers to use all the techniques of selective breeding to produce human individuals with a desired genotype. This paper aims to draw the attention of other scholars to this dramatic and—to some, at least—potentially disturbing new technological possibility.

PROSPECTS FOR *IN VITRO* GAMETOGENESIS

Scientists have now succeeded in producing sperm and oocytes from embryonic stem-cell lines in mice[2, 3, 7-11] and have used both the sperm[2,12] and the eggs[3] to produce offspring. Researchers have also succeeded in deriving primordial germ cells from (murine) induced pluripotent stem (iPS) cells[13], and in producing functional sperm[2] and eggs[3] from primordial germ cells generated from (murine) iPS cells, effectively removing the distinction between somatic and germ cells when it comes to the (technologically mediated) reproduction of the organism. More recently, researchers have begun to publish some results involving the production of gamete-*like* cells from both embryonic and induced pluripotent human stem cells.[14-16] Moreover, it is clear that rapid progress is being made in the field.[17] A number of sober commentators are now predicting that it will eventually be possible to produce functional human gametes from pluripotent stem cells.[1, 4, 17] It is therefore worth beginning to think about the reproductive scenarios and ethical issues that will arise should this possibility eventuate.

BREEDING HUMAN BEINGS *IN VITRO*

As I noted at the outset, the development of a technology of *in vitro* gametogenesis would have many applications as a powerful new reproductive technology. If it proves possible to derive gametes from induced pluripotent stem cells, or from embryonic stem cells derived from embryos created by (hypothetical) somatic cell nuclear transfer, this would allow the creation of the genetic offspring of any person from whom a somatic cell containing nuclear DNA could be sourced.[iii] Thus, *in vitro* gametogenesis could serve as a powerful new technology to overcome infertility, especially for men who are unable to produce viable sperm, women who have undergone premature menopause, and for those who have lost their

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and is the first full-length consideration of the challenges that will need to be overcome before it will be possible to use *in vitro* gametogenesis to breed human beings *in vitro*.

[iii] Although see Mertes and Pennings for an argument to the conclusion that the use of artificial gametes would have much less utility for achieving genetic parenthood than would first appear.[18]

gonads due to injury or had them removed in the course of cancer treatment. These applications are likely to drive the search for a reliable technology of *in vitro* gametogenesis. Perhaps more controversially, *in vitro* gametogenesis would also allow post- menopausal women and women pre-menarche to become genetic mothers and for posthumous reproduction even in the absence of stored gametes: it might even allow men to become genetic mothers.[19-20][iv]

The ethical issues raised by these possibilities have been discussed elsewhere (See, for example:[4, 19, 21-24]) and are not my concern here. Instead, I wish to raise awareness of the possibilities that this technology offers to investigate and to shape the human genome. It is already possible to derive stem cells from human embryos[25-26] and to create stem cells by inducing pluripotency in human somatic cells.[27] If it becomes possible to derive functional gametes from stem cells then it will also be possible to fuse these gametes with gametes derived from another stem cell line to create embryos from which new stem cells may be derived – from which new gametes can be derived.[28] This process of iteration might allow scientists to proceed forward through multiple generations of human beings "*in vitro*". It could also allow researchers to apply all the techniques of selective breeding to the human species without needing to persuade anyone of their mate choice and without fear of violating reproductive liberty. By choosing to fertilise eggs derived from (stem cells derived from) selected embryos with sperm derived from (stem cells derived from) other selected embryos over several generations, researchers could try to ensure the creation and combination of desired genotypes.[v] In order to address any concerns about inbreeding, they could introduce new genes and further genetic diversity as required by sourcing new stem cell lines from donated embryos (or from donated somatic cells via cellular reprogramming) or simply new (donated) gametes. Of course, at any stage they could also choose to implant any of the embryos created—or clones thereof, produced via embryo splitting—into the womb of a willing woman, with the intention of bringing it to term.

[iv] The role played by the Y-chromosome in spermatogenesis suggest that it will not be possible to produce sperm from stem cells derived from somatic cells taken from the bodies of women: it may well be possible to produce oocytes from stem cells derived from somatic cells taken from the bodies of men. The creation of a "mouse with two mothers" demonstrates that there is also a theoretical possibility of the creation of a new individual from two oocytes, which would allow two women to become the "genetic mothers" of a child.[29]

[v] Cryopreserving either embryos or gametes would allow researchers to cross embryos with embryos of any previous generation, significantly increasing the power of this type of breeding as compared to most programs of artificial breeding using sexually mature organisms.

The prospect of being able to breed human beings "*in vitro*" raises many ethical issues. [vi] Before we can begin to discuss these, however, it is important that we first have as clear a sense as we can about the power and limits of this technology. Thus, before moving to discuss the various applications of *in vitro* eugenics, I want first to highlight the existence of one practical barrier to the development and application of this technology, one immediate ethical barrier, and two practical limits on its applications. Unless the practical and ethical barriers can be overcome, *in vitro* eugenics will never get off the ground. The practical limits suggest that *in vitro* eugenics is unlikely to be *quite* as powerful as might first appear.

A practical barrier

The practical barrier concerns the risk that maintaining cell lines *in vitro* will lead to epigenetic changes that may be transmitted via gametes derived from these cell lines to the next generation of embryos.[vii] The possibility of epigenetic changes impacting on gametogenesis is a barrier to the creation of gametes for reproductive purposes from stem cells. Scientists will need to be confident that the gametes they produce have normal chromatin and patterns of methylation before it would be ethical to contemplate using them for reproductive purposes.[viii] However, the iterative process involved in *in vitro* eugenics raises the possibility that small changes that might not affect the viability of gametes produced in a single iteration might accumulate over multiple generations until gametogenesis is no longer possible or such that it would be irresponsible to use the embryos created for reproductive purposes.

It is obviously not possible to determine in advance whether such epigenetic changes will render *in vitro* eugenics impossible: we will have to wait and see what the science suggests.

[vi] Note that I am *not* claiming that the embryos that would be created in this process are human "persons," in the philosophical sense; nor do I intend to imply anything about the moral status of embryos. Nevertheless, my characterisation of this process as "breeding human beings" will, inevitably, be controversial. In particular, Jeff McMahan has argued that both that human individuals do not begin as embryos and that early-stage human embryos are not human organisms.[30] However, given that the embryos involved in this process will be human embryos (as opposed to goat or squid embryos, for instance) and that my primary interest here is in the potential use of *in vitro* eugenics to bring into existence individuals with character traits that would be the result of a multi-generation process of selective breeding—and in order to avoid the incongruity of writing of "multiple generations of human embryos" in various places—I have chosen to proceed with the formulation offered here. Those who are particularly moved by McMahan's arguments may wish to substitute "breeding human embryos" where appropriate.

[vii] For discussion of the current state of the science concerning the heritability of epigenetic changes and the mechanisms of intergenerational transmission of such changes, see Daxinger and Whitelaw, and Skinner.[32-33] My thanks to Patrick Western for drawing my attention to these sources.

[viii] Although see below for discussion of just how demanding the requirement that new uses of reproductive technologies be "safe" really is.

The fact that (most) epigenetic marks are reset in the development of the germline[31] gives some cause to hope that epigenetic errors might be corrected each time a new generation is created—although there is no guarantee that errors will not creep into this process as well. However, it is worth observing that the fact that scientists will need to be able to evaluate the genetic and epigenetic quality of gametes produced by *in vitro* gametogenesis in order to use these for reproductive purposes does at least suggest that this same quality check could be employed to reduce the likelihood of the transmission of errors in each generation and also to check the quality of any gametes used to produce embryos for reproductive purposes at the end of the process.

An ethical barrier

The ethical barrier to *in vitro* eugenics arises because both the development and application of this technology would involve the deliberate creation of embryos for the purpose of research, something that is currently against the law in a number of jurisdictions.[4] Human embryos are, of course, entities whose moral status is intensely contested. Even authors who have been inclined to deny that embryos should be granted the same moral status as (other) human beings, have often allowed that there are some moral limits on the uses to which embryos may be put and, in particular, on the purposes for which they may be brought into existence.[34] In many polities, the creation of embryos outside of the human body for reproductive purposes has been accepted, presumably because reproduction is seen as a project of great value, whereas the creation of embryos for other purposes has not been endorsed, because of concerns about the social consequences of the "commodification" of embryos or because divorcing the creation of embryos from the context of reproduction would fail to demonstrate appropriate respect for the value of embryos.[35] For this reason, research involving human embryos—including the derivation of stem-cell lines—has typically been carried out on "surplus" embryos created for the purpose of reproduction in IVF programs and then donated for research.[ix]

However, the development of the technology for *in vitro* eugenics would require the creation of embryos without any intention of using them in reproduction, in particular in order to show that the level of risk involved in bringing embryos created through this technology to term (of which, more below) is acceptable. Moreover, as I will discuss further below, one of the main

[ix] The grounds and the plausibility of a distinction between the ethics of creating embryos for research and the ethics of research on "surplus embryos" created in the course of the pursuit of a live birth using IVF have been the subject of much bioethical controversy. For a useful introductory discussion, see Robertson.[36]

applications of this technology would be for research, to learn more about human genetics and disease. Even where the intention of those employing *in vitro* eugenics *was* to bring new individuals into existence, this would still require the creation and destruction of multiple embryos in the course of the process of selective breeding. Thus, the prohibition of the creation of embryos for research purposes *will* stand as an insurmountable barrier to the development of the technology of *in vitro* eugenics in jurisdictions where it exists.

Yet the prospect of *in vitro* gametogenesis also provides us with strong reason to believe that this prohibition is likely to be eroded or abandoned in the not-too-distant future. In order to demonstrate that gamete-like cells produced from human stem cells are in fact capable of successfully fusing to create a new embryo, and in order to prove that embryos created using artificial gametes will develop normally, it will be necessary to create human embryos *in vitro* and examine them for karyotypic, genetic, and epigenetic abnormalities. Such testing would be essential before it would be ethical to use artificial gametes for reproductive purposes.[4][x] Because of the potential of *in vitro* gametogenesis to serve as a powerful new technology to overcome infertility, especially for men who are unable to produce viable sperm, women who have undergone premature menopause, and for those who have lost their gonads due to injury or had them removed in the course of cancer treatment, there is likely to arise very significant political pressure to allow the creation of embryos for research purposes in order to test *this* technology.[xi] Thus, it seems likely that by the time *in vitro* eugenics becomes possible any prohibition on the creation of embryos for research purposes will have already been rescinded.

Practical limits

The first *practical* limit concerns the amount of time that is likely to be required to move forward a generation "*in vitro*". While this will undoubtedly be an order of magnitude less than the 13 years that is currently required to produce a new generation of human beings, the power of *in vitro* eugenics will be significantly affected by just how much time is involved. There are four processes that will need to take place in each generation, each of which may be expected to take a certain amount of time. First—assuming that we identify the beginning

[x] Research using animal models might go some way towards demonstrating proof-of-concept but assessment of the safety of the use of *in vitro* derived human gametes will require demonstrating – at the very least – that they are capable of generating phenotypically normal human embryos *in vitro*.
[xi] The development of a viable technology of *in vitro* gametogenesis would in fact expand the number of people who might become genetic parents to include anyone from whom a tissue sample may be sourced.

of the process as the derivation of gametes—it will be necessary to derive gametes from stem cells that are being maintained *in vitro*. As we do not yet know the details of a reliable protocol for *in vitro* gametogenesis from human cells, it is not possible to place a precise figure on how long this is likely to take. However, as spermatogenesis takes approximately 70 days *in vivo*, this suggests an upper limit on this process: it is possible that *in vitro* derivation of sperm might be achieved in as little as 35 days. Derivation of oocytes may take significantly longer, as the maturation of oocytes *in vivo* takes approximately six months.[37] However, again, it is possible that *in vitro* derivation might be possible within a shorter timeframe.[38] Second, sperm and egg must be united, fuse, and a new embryo develop until the blastocyst stage in order that new stem cells may be derived from this embryo. This will require 7 days. Third, the stem cells taken from the inner cell mass of the embryo must be coaxed into developing into a colony suitable for use in the derivation of further gametes. Again, precisely how long this will take will depend upon the details of the protocols for the derivation of gametes and, in particular, how many stem cells are required and of what quality. A plausible estimate of the *minimum* time it might take to produce the required stem cells is 28 days, but if a stable and well-characterised line of stem cells is required, this may require a number of months. Fourth, researchers must characterise the genotypes of the embryos (or stem-cell lines) created in each generation and decide which embryos should be selected to be used to begin the task of breeding the next generation. Modern gene-sequencing technologies mean that it should be possible to characterise the genotype concurrently with the third process, but how long it will take to decide which genetic lines to cross will depend upon the skills and resources available to the scientific team conducting the breeding.

Although there are significant uncertainties in several of the estimates provided above, "four-to-six months" seems plausible as an initial estimate of the amount of time that might be necessary to proceed forward a generation "*in vitro*". If this is correct, researchers could produce two or three generations of human embryos each year using the procedure I have described. While this figure places significant limits on how radical a transformation of the human genome might be possible through selective crosses using this technology, it is also clear that an *in vitro* breeding program of this sort would give future eugenicists a power undreamed-of by governments and would-be genetic reformers of the past. In a ten-year research program, scientists might produce twenty to thirty generations of human beings *in vitro*—enough to achieve significant changes in genotype. Advances in cell culture

technology and in the science of gametogenesis might increase this figure still further. Obviously, the more generations it is possible to proceed through each year, the more powerful this technology will become.

The second practical limit on the technology arises out of the difficulties involved in performing the last task described above, i.e. in deciding which embryos to use in selective breeding once several generations have been produced. It is one thing to be able to identify—or even cross *in vitro* to produce—certain genotypes, it is quite another to know which genotypes we should be aiming to produce. The power of *in vitro* eugenics will therefore be a function of our ability to understand specific genotype/phenotype correlations and, more generally, of our understanding of human genetics. Of course, our understanding of human genetics has increased rapidly over the last several decades, especially since the completion of the human genome project, and is likely to increase further over coming years. Indeed, as I will discuss below, one application of *in vitro* eugenics is precisely to serve as a valuable tool to investigate the operation of particular genes. Nevertheless, the utility of *in vitro* eugenics for producing a desired phenotype will be limited unless we know what genes—and in which combinations—are involved in producing it.[xii]

THREE APPLICATIONS

Despite the limitations I have discussed here, should it prove possible, *in vitro* eugenics might have three valuable applications: as a tool to research the heredity of genetic disorders; as a means by which to produce cell lines with particular genotypes for research and therapeutic purposes; and, as a method to bring into existence children with a desired genotype.

Research into the heredity of genetic disorders

The most immediate scientific application of this technology—and the reason why it is likely to be developed—is for research into the heritability and development of various genetic disorders.[4] Rather than—or perhaps more realistically, in addition to—relying upon epidemiological and historical evidence, which is often difficult to gather and unreliable when it does exist, to investigate the transmission of genes suspected of involvement in the etiology of a particular disorder, researchers could perform genealogical experiments in the

[xii] It is worth observing that this caveat applies equally to all the technologies that have been discussed as methods of producing genetically modified human beings. In the context of the large literature on the ethics of human genetic enhancement, it would be unfair to single out *in vitro* eugenics for the criticism that it presumes a knowledge of genetics that we currently lack and may never in fact acquire.

laboratory. Fusing gametes derived from stem cells derived from embryos that carry a gene that is known to be associated with a particular genetic disorder would allow researchers to investigate how such disorders are inherited and to investigate the contribution that different genes make to the disorder. Indeed, by allowing researchers to breed embryos with different genotypes, this technique would allow them to test hypotheses about the role of different genes in various disorders. *In vitro* eugenics might therefore make a valuable contribution to our understanding of genetics and disease and thus to the quality of genetic counselling and therapeutic interventions available in the future.

Production of cell lines with specific genotypes

According to Mathews et al., *in vitro* eugenics might also serve as a valuable tool for producing cell lines containing a particular genetic mutation or set of mutations, which could in turn serve as a means to study the progression of the resulting genetic condition or to test drug therapies to ameliorate it.[4] Similarly, researchers might be able to develop (through selective crossing) cell lines that were suitable for use for therapeutic purposes in a wide range of individuals by virtue of having appropriate Human Leukocyte Antigen (HLA) tissue-typing or other desirable properties.[4] According to Mathews et al., then, *in vitro* eugenics holds out the prospect of results that may translate into clinical applications, in the form of drug and cell therapies, with significant benefits to future generations.[4] If this is true, the possibility of these future benefits is a strong argument in favour of pursuing *in vitro* eugenics. [xiii]

Breeding better babies

Once researchers have succeeded in creating several generations of embryos in the laboratory in the course of researching the genetics of disease, a question will inevitably arise about implanting embryos created through *in vitro* eugenics into the womb of a woman in order to bring a new individual into the world. Moreover, this question is likely to arise with some urgency because of the potential of *in vitro* eugenics to serve as a powerful technology of

[xiii] It must be acknowledged that there are already available alternative means of achieving both the ends discussed here, which Mathews et al. do not address.[4] The transcription-factor induced reprogramming of somatic cells allows the creation of cell lines with specific genotypes, while in recent years advances in tissue typing, tissue banking, immunosuppressive therapies and adoptive immunotherapy have greatly reduced the difficulties involved in finding a sufficient HLA-match to allow successful transplantation of most tissues. These observations suggest that the case for the utility of *in vitro* eugenics may rest more on its applications as a reproductive technology than Mathews et al. allow.[4] My thanks to Giuseppe Testa, Patrick Western, and Ian Kerridge for encouraging me to appreciate the force of this objection.

"human enhancement". If it becomes possible to breed human beings *in vitro*, it will be possible to use all of the techniques of artificial selection to produce embryos with desirable genomes. In effect, scientists will be able to breed human beings with the same (or greater) degree of sophistication with which we currently breed plants and animals. Importantly, there are currently several influential bioethicists who argue that we are morally obligated—or, at least, have strong moral reasons to—enhance future human beings.[39-42] Implanting embryos that have been bred for above-species-typical capacities into the wombs of willing women would be one way to achieve this goal.

In vitro eugenics would be *most* powerful if it becomes possible to produce viable gametes from induced pluripotent stem cells. In this case, it would be relatively straightforward to gather a suitable "stock" with which to begin the breeding program—and from which to introduce new genes into the process at any point as required in order to avoid concerns about "inbreeding"— by sourcing somatic cells from a large number of individuals with desirable genetic traits and then deriving stem cells and then gametes from these. However, it would also be possible—although more difficult—to gather the stock for the breeding program in the form of embryonic stem-cell lines created by other researchers or in the form of embryos donated through IVF programs. Indeed, presuming the restriction on the creation of embryos for research is lifted, it would also be possible to begin (or to introduce new sources of genetic diversity at any stage) simply by using donated gametes.

Again, it is important to acknowledge that there are likely to be significant limits on our capacity to use this technology to produce intended outcomes due to the limits of our knowledge of human genetics. As the vast majority of desirable phenotypes will be the result of complex interactions involving multiple genes in particular environments, it may be very difficult to determine what genotypes we should be aiming to produce *in vitro*. Attempts to combine genes associated with desirable phenotypes in one genome may have unanticipated consequences due to interactions between the genes or other sequences that may have been combined alongside them. Moreover, while it may be possible glean some information about the phenotype likely to result from a given genotype by using theoretical models of gene activity and by drawing upon population level studies of genetics, ultimately the only way to

determine whether a given genome will produce a child with enhanced capacities will be to bring a child into existence and study them over their lifetime.[xiv]

Despite these caveats, *in vitro* eugenics is likely to be superior to the other technologies that have been proposed as methods to enhance the genetics of future human beings—namely preimplantation genetic diagnosis (PGD), somatic cell nuclear transfer (SCNT) cloning, and recombinant-DNA technology.

PGD allows prospective parents to choose amongst embryos they have created via IVF on the basis of their genetics before implanting their chosen embryo(s) into the woman's womb: they may therefore use PGD to "enhance" their children if they are able to select embryos with genes for above-species-typical traits. SCNT cloning would facilitate enhancement by allowing scientists to bring children into the world who had the same genome as an individual identified as possessing a superior genotype. Yet both these technologies are limited in so far as the range of enhancements they make possible is restricted to those that arise by chance through the recombination of genes during meiosis and the mixing of the recombined genomes at fertilisation.[xv] *In vitro* eugenics would allow researchers to consciously shape the human genome by combining (through selective breeding) desirable traits that arise in different embryos.[xvi]

Recombinant-DNA technology would also allow scientists to achieve enhancements that have not arisen (and perhaps would not have arisen) by chance. However, the utility of this technology as a method of human enhancement is constrained by the difficulties involved in introducing new genes into a location in the genome where they will achieve their intended results without disrupting the activities of other genetic systems and of being confident of their effects in the functioning organism. The development of iPS cells has, admittedly, greatly increased the potential of recombinant-DNA technology. If they wished, researchers could now attempt to introduce novel or trans-species genetic sequences into human cells maintained in a colony of stem cells, vastly increasing the chances that some cells at least will integrate the desired sequence into the target location. Cellular marking technology

[xiv] Again, this limitation is a feature of any attempt to produce desired traits in human beings through genetic manipulations.

[xv] If it becomes possible to produce gametes from induced pluripotent stem cells, this will dramatically increase the power of PGD by removing the limit currently imposed on the technology by the small number of oocytes that may be salvaged in each cycle of IVF.[6]

[xvi] *In vitro* eugenics would have the further advantage over SCNT cloning that it would create organisms with normal telomeres, rather than the shortened telomeres associated with cloning. My thanks to Jeremy Brownlie for drawing this virtue of the technology to my attention.

would allow researchers to identify and cultivate these cells, which could then be fused into tetraploid embryos in order to create a clone of the individual from whom the original stem cells were sourced, but with a modified genome. Alternatively, having created genetically modified stem cells, gametes could then be derived from these and fused with other gametes to create embryos that would include the modified gene.[19-20] Even with these advances, however, the use of recombinant-DNA technology to modify the human genome will remain an extremely uncertain and risky proposition.

In vitro eugenics is, in theory, a less powerful technology than recombinant-DNA technology– the latter would allow scientists to engineer modifications by using genes drawn from other species—but is likely to be a much more reliable technology in practice and one that will still allow significant modification of the human genome. The practical advantages of *in vitro* eugenics derive from the fact that (most) genomic imprints are reset in the course of the formation of the germline and in the early stages of the development of the zygote[31] and from the capacity of the processes of meiosis and fertilisation to screen out (some of the) genetic errors that would be lethal to the organism. In choosing at each stage to proceed with viable gametes derived from viable embryos, researchers would introduce a crucial selective process that could function to reduce the probability that epigenetic changes or novel combinations of genes would have deleterious effects on the functioning of the organism. Moreover, in so far as *in vitro* eugenics would mimic sequences of fertilisations that might have occurred in the natural course of human reproduction, researchers have more models and a better evidence base to draw upon to try to evaluate the impact of novel combinations of genes produced by this technique. *In vitro* eugenics is therefore likely to be less risky than the use of recombinant-DNA technology to modify embryos.[xvii]

Safety

Although *in vitro* eugenics has these advantages over PGD, SCNT, and recombinant-DNA technology, there remains an obvious objection to the creation of new individuals by *in vitro* eugenics—as there is to any new reproductive technology—that derives from the experimental nature of the technology when it is first used. How could we know that this

[xvii] It is also worth observing that *in vitro* eugenics might be used in combination with recombinant-DNA technology to create an even more powerful technology. Employing the two technologies together would allow scientists to create embryos that possess multiple modified traits by combining individual modifications that had been achieved using recombinant DNA technology in different embryos or cell lines through a process of selective crossing.

technology is safe? That is, how could we know that it will be possible to bring the embryos created through *in vitro* eugenics to term and that the individuals who developed from these embryos will not suffer increased risks of ill health as a result of the circumstances of their conception? These questions loom especially large because of the concerns about possible variations in the epigenetics of embryos created via *in vitro* eugenics, discussed above. While it may be possible to check that embryos created via *in vitro* eugenics develop "normally" *in vitro* and to go some way towards trialling the technology in animal models, the first uses of embryos created by *in vitro* eugenics to try to achieve a live human birth will necessarily be experimental.

However, there are a number of reasons to believe that concerns about safety and risk are unlikely to prove an insurmountable barrier to the ethical creation of designer babies by *in vitro* eugenics. To begin with, as I noted above, these concerns arise regarding every new reproductive technology involving the manipulation of embryos. Until a generation of children produced by IVF (or intracytoplasmic sperm injection or cytoplasmic transfer) have lived out their natural lifespan, we will not know whether IVF (or any of these other technologies) is safe—and we certainly did not know this at the time at which those technologies were first trialled.[xviii] Thus, *in vitro* eugenics would not raise any issues we have not confronted before. Moreover, it seems unlikely that we must be sure that *in vitro* eugenics must be completely devoid of risk before it would be ethical to trial it. "Natural" conception and pregnancy involves many risks but we do not think it unethical to seek to become pregnant by natural means.[19] Finally, although the claim is controversial, it may be argued that it would be ethical to use even reproductive technologies with significant risks given that, as long as children are born with sufficient quality of life that it is not rational for them to prefer to be dead, these individuals will not be able to claim that they were harmed by the mechanism of their birth—on the grounds that they would not have existed at all except for the use of the technology.[43] Concerns about safety and risk are therefore unlikely to rule out the ethical creation of children by *in vitro* eugenics, once animal and laboratory testing has shown that the technology has a reasonable chance of producing children with a reasonable quality of life.

[xviii] For a recent survey of the (parlous) state of knowledge about the risks involved in assisted reproductive technologies, see Allen et al.[44] For concerns about the effects of epigenetic modification during cytoplasmic transfer see Hawes et al.[45]

CONCLUSION: *IN VITRO* EUGENICS AND THE ENHANCEMENT DEBATE

I have endeavoured here to provide a detailed and realistic account of the prospects for *in vitro* eugenics. However, it must be admitted that *in vitro* eugenics is at least two large steps removed from the current state of the science of human reproduction. First, scientists must achieve the derivation of functional gametes from human stem cells *then* they must show that this technology can be used iteratively as I have outlined here. We do not yet know whether either of these things will prove to be possible, nor do we have a reliable means of estimating the timeframe by which they might come about if they are. One might therefore wonder about the wisdom of spending too much time thinking about the ethics of this technology at this point.

However, as I noted above, authorities in the field *do* expect that *in vitro* gametogenesis will eventually be possible in humans. As I have argued here, barring problems with epigenetic modification, the possibility of the iterative use of the technology then follows relatively straightforwardly. Given the number of ethical issues *in vitro* eugenics would raise—and their complexity—it would seem prudent to begin thinking about them sooner rather than later. Moreover, given that there is currently a vigorous debate about the ethics of human enhancement going on in the bioethical literature (which—it is worth observing—regularly discusses ethical issues arising out of technologies that are equally if not more speculative than the one I have described here) and given the enormous potential of *in vitro* eugenics as a technology of human enhancement, it would appear that *in vitro* eugenics should move to the foreground of this debate. The current paper, which has attempted to describe the potential and limits of this technology, is intended to encourage and facilitate the ethical discussions that will be essential if we are to choose wisely about the development and uses of "*in vitro* eugenics."

POSTSCRIPT: CHILDREN OF THE LAB

As I have argued elsewhere, any children born as a result of the fusion of gametes derived from stem cells derived from embryos would be "orphaned at conception".[28] That is to say that, they would have no genetic parents: there would be no living individual—or indeed individual that had ever lived—who could be described as the genetic progenitor of such embryos. They may, of course, have genetic grandparents or great grandparents or great,

great, grandparents, etc, but with each successive *in vitro* generation the genetic links between the embryos involved and their living ancestors would become weaker and weaker.

This lack of genetic parents might be thought to expose children created by *in vitro* eugenics to psychological risks. However, claims about the psychological impact of these strange circumstances are necessarily speculative: elsewhere, I have argued that it in fact be might be better to be born without genetic parents than to know that one had genetic parents who abandoned one.[28] In any case, the evidence from the history of IVF and artificial insemination by donor suggests that adequate love and care from their *social* parents is sufficient to allow children to flourish socially and psychologically.[46-48][xix]

However, the fact that children born of *in vitro* eugenics would be "orphaned at conception" has important implications for the extent to which *in vitro* eugenics might fulfil a useful role as a technology of assisted reproduction. Given that adoption or the use of donor gametes (and—if necessary—a surrogate mother) will allow any individual to become a *social* parent, the justification for the development and use of more sophisticated reproductive technologies relies upon the importance many people place on achieving *genetic* parenthood. While *in vitro* gametogenesis has an enormous potential as a method to allow individuals to become genetic parents,[xx] *in vitro* eugenics offers nothing in this regard. Thus, the justification (if any) for using *in vitro* eugenics to bring new individuals into the world must rely upon its potential to serve as a technology of human enhancement.

Interestingly, Julian Savulescu, one of the leading advocates of an obligation to enhance, limits this obligation to the production of the best children we can *who would be our genetic offspring*.[42] Elsewhere I have argued that this caveat is unprincipled and that the reasons Savulescu adumbrates for enhancing "our" children are also reasons for bringing children into existence that have no genetic relation to us.[49] If Savulescu is correct and we have no obligation to bring enhanced individuals into the world *per se* but only to enhance "our" (genetic) children, then *in vitro* eugenics would <u>not</u> be a useful technology for human enhancement, as the children it produced would have at most a tenuous genetic relationship to the people who brought them into the world. On the other hand, if our reasons for

[xix] But for an argument that it is immoral to bring into existence children who will be alienated from their genetic relations, see Velleman.[50] Velleman's arguments, if correct, stand as a substantial objection to the use of *in vitro eugenics* to bring children into existence, as they do to the use of donor gametes from anonymous donors.

[xx] But again, compare Mertes and Pennings.[18]

enhancement concern the welfare of future individuals then, given that *in vitro* eugenics might produce individuals with significantly "enhanced" genomes, it seems that advocates of enhancement should argue that parents have strong moral reasons to choose to have children created by this means. If nothing else, then, the possibility of *in vitro* eugenics serves as an illuminating test case for the implications and plausibility of arguments about the nature of our reasons to pursue human enhancement.[xxi]

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