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COMMENTARY

How genetics human ART style is making dreams come true: the stairway to eugenics

David F. Albertini[1]

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Turning the course of history around after the events of the past 4 years will be, to say the least, a task of daunting proportions. Among the many problems on the agenda—setting aside pandemics, the loss of biological diversity, and global warming—is a misguided and maligned biomedical enterprise. The loss of public trust, the misuse of emerging technologies, and the blatant disregard of the human condition all contribute to an imperative for change. That reproductive medicine and biology are at the very center of much of what is wrong about the way science is proceeding is now an understatement.

In the September 1924 issue of The Journal of Social Forces (https://academic.oup.com/sf/article-abstract/2/5/770/1991435), a review of J.B.S. Haldane's recently published *Daedalus, or Science and the Future* comments:

"…. (with) the whole nation urbanized and the race reproduced by means of artificial fertilization of ova developed in vitro he (Haldane) reminds one of Jules Verne at his best. His work may be taken as more as an imaginative dream of what a super-science may accomplish rather than what it seems likely, in view of immediate prospects, to accomplish. And yet it is impossible to deny that all of his dream or the equal of it may some day come true."

While Haldane the scientist is credited with many ideas that would influence among others the unlikely duo of Aldous Huxley of *Brave New World* fame and Gregory Pincus, the first to demonstrate mammalian egg parthenogenesis (and oocyte in vitro maturation), his contributions to the prevention of aging with hormones, controlling behavior with drugs, and making and sustaining human embryos in vitro (*ectogenesis* he called it) were far more than conceptual platforms upon which science would translate into reality. Haldane's prescience with respect to human ARTs was one thing; his contributions to the then nascent field of human genetics were quite another, spawning much to his dismay, what would become the eugenics movement of the nineteenth century introduced by Sir Francis Galton.

As Judith Daar elaborates in her book *The New Eugenics: Selective breeding in an era of reproductive technologies* (2017 Yale University Press; New Haven and London. ISBN 978-0-300-13,715-6), the not-so-orderly transformation of biological inquiry into the treatment and diagnosis of infertility involved many players, Edwards and Steptoe and the Jones' as we know. But as she reveals in the context of ethics, law, and social justice, the consequences of what human ARTs has become looms larger at the interface of science and society today than could ever have been anticipated in 1978.

This issue of JARG brings to light current matters of interest regarding eugenics and traces for our readership a relatively recent, but woefully incomplete, history, of how reproductive genetics in the context of human ARTs has delivered our field to a place in society we need to be better prepared for (*www.axios.com/gene-editing-and-the-uncertain-future-of-human-reproduction-50f7885c-d2b3-4113-be86-aebfed3beb82.html*).

We begin with a Nature commentary that captured my attention a few years back. Amidst all the hoopla surrounding the 150th anniversary of Mendel's pea experiments, Professor Gregory Radick queried whether the teaching of genetics today might have appeared differently if the train ride to contemporary genetics had taken a different path. As a historian of science, he has dedicated a career to understanding the influence of "counterfactual" science on current day curricula used by students in their formative years of training, or even as professionals raised on and continually fed by a diet of good-old Mendelian genetics [1].

If you are at all doubtful about how human ARTs today has played directly into the hands of eugenics, then have a close look at two articles featured this month. The first, a Delphi survey by Professor Alon and colleagues from Israel and

✉ David F. Albertini
eicjarg@gmail.com

[1] Bedford Research Foundation, Bedford, MA, USA

Spain, is part of the preparation process alluded to above in asking just how our present day practices of sorting facts from fiction may appear down the road a bit and into the future (*Regulating reproductive genetic services: dealing with spiral-shaped processes and techno-scientific imaginaries;* https://doi.org/10.1007/s10815-020-02017). No surprises here that PGT retains its lofty and yet listless position in the debate. The second paper of note is a commentary from a distinguished group of Italian clinicians and scientists representing two national societies, and importantly drawing our attention to the dilemma of embryo selection when faced with the legal restrictions they are bound to (*When embryology meets genetics: the definition of developmentally incompetent preimplantation embryos (DIPE)—the consensus of two Italian scientific societies;* https://doi.org/10.1007/s10815-020-02015). Cimadano and colleagues have done a great service to the reproductive medicine community in providing a thoughtful and compelling treatment of a subject that extends well beyond attending to the complexities and nuances of practicing ARTs in Italy. Elaborating on the confluence of "embryology and genetics" in terms of "developmentally incompetent preimplantation embryos" (DIPE not DUPE), they effectively expose and espouse exactly what Bob Edwards hoped would never happen when first entertaining the concept of PGD. It should be remembered that the impetus for making human oocyte cryopreservation the clinical and societal force that it is today stemmed from legal restrictions imposed on ART practice—in Italy—over 20 years ago. The stimulus for change takes on interesting twists of fate.

With a bandwidth stretching from Haldane's ectogenesis to Mendel's peas, to Edwards' melding of genetics and reproductive technology, what can we say frankly about the place human ARTs now occupies in society today? Time for some woefully incomplete historical reflections on how we got here in the first place!

Not surprisingly given Edwards nurturing and nudging, ESHRE maintained a vigilant and diligent role as gatekeeper and educator as PGD metamorphosed from its humble origins to a genome-era technology; consistently since the early on recognition of the limitations of FISH as a valid diagnostic, ESHRE has remained wary of the potential uses and abuses of genetic testing strategies as technology progressed [2]. Voices of reason have made more than marginal comment on the more contemporaneous melding of clinical disciplines and technology. Consider that what started as PGD for detection of monogenic disorders in affected individuals evolved into all of the PGTs as we know them today, in parallel with the advent and introduction of gene editing, and spindle transfer/mitochondrial replacement strategies, together bolstering in essence the "curative" wonders made possible by ARTs [3]. What "counterfactual" scientific contributions or investigational behaviors may be enabling a plausible eugenics movement today?

Enter the PGT controversy. Built firmly upon the notion that aneuploidy was a root cause of reproductive failure in humans, new genetic testing platforms had to be developed that would eventually usurp the previous standard of care eliciting what I like to refer to as the "mywayisbetterthanyourway" mindset [4]. From the binary nature of PGT-A to the "percentages matter" disposition of mosaicism, and the hedging of bets after the rebirth of self-correction, publications finally arrived partially resolving at least one thing after years of contentious discourse [5, 6]. Many of the embryos stored in those Italian freezers may not be incompetent after all (DIPE) but rather constitute developmentally unable preimplantation embryos (DUPE) because they are sitting in liquid nitrogen, …or are unable to progress because of the way we procured and treated gametes or embryos, …. or they exhibited too much fragmentation-and the list goes on. Fact is we practitioners have been duped into believing what a few leaders in our field have been saying over the past decade or two while maintaining a Mendelian perspective of human genetics that is both outdated and misused by and for stakeholders. Somehow, even the purveyors and drivers in the field of CRISPR-based gene editing have seen and are practicing caution and discretion when it comes to clinical application [7]. Can we learn a lesson or two from history, one distal (>100 years) and one more proximal (<10 years).

Haldane's concept of ectogenesis proposed a limited extent of ex vivo development for human embryos—owing in part to the fact that embryo transfer in animals was being attempted, if not yet accomplished. Fast forward to 2020 and a truncated version becomes the standard of care in human ARTs (lest we entertain what this organoid business is all about). To be fair, as many of us elders well know, practice patterns changed over the years.

What started as GIFT and ZIFT soon evolved into traditional IVF and transfer of embryos at an early stage. While not practical today, GIFT and ZIFT did skirt around some of the ethical issues of yesteryear and some would still contend that reuniting conceptus and reproductive tract at the earliest possible occasion might even recapitulate some aspects of biology that ART has not quite yet figured out.

Even so, the more recent drive towards ectogenesis happened for any number of reasons, sensible or not. First, there was the case, binarized for public consumption, of when to best sample the embryo's genotype by a biopsy at the cleavage or blastocyst stage. Blastocyst wins [8]. Then, what combination of biopsy and testing platform would yield the kind of implantation AND live birth rates indicating we were on the right track? Human embryos—specifically blastocysts—could handle a prick or two and sorting the good and the bad genetically speaking was well within our goals for the future [9]. Hard to believe that was back in 2013.

Despite the continued emphasis on PGT-A, or because of it, deliberations over genetics as a sole tool for embryo selection had to contend with not simply the matter of whether a

poke or two had an adverse effect on future outcome but what was embedded within the embryologists' toolbox that might complement what was becoming a "deselection" mentality. To wit, going from we-knew-what-we-selected was right to narrowing down the list to the best possible candidates for making a baby. Enter time-lapse imaging/morphokinetics and artificial intelligence. As so eloquently stated by the late Yogi Berra:

"If you don't know where you are going, you might wind up someplace else".

Someplace else it was. Making the difficult choices came down to discarding embryos harboring chromosomal aberrations that may or may not contribute to the definition of DIPE, or most importantly the birth of a child to wanton parents. This difficult question was taken to heart in an opinion piece published by the Ethics Committee of the ASRM in 2017 [10]. Much has changed since then that will continue to influence practice policy design and implementation among clinics especially in the USA where an ongoing reliance on guidance from the organizations like the ASRM will bring to the forefront all matters societal, legal, and ethical [11].

In the end, making dreams come true for the infertile couple has been and will continue to be both the mystery and the magic of human ARTs. More than anything else, the fragile and tenuous nature of science and society must be thoughtfully recognized and acted upon by reproductive medicine specialists once some level of acceptance that genetics in 2021 is not what it used to be. Until our inherent biases can be managed in an environment respectful of the shortcomings of past and present science, the link between human ARTs and eugenics will only grow stronger.

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