The Almost Perfect Baby

Genetics, reproduction, and eugenics

By Jean-Hugues Déchaux

The genetic revolution is marked, in particular, by complex transformations in reproductive technologies. From our relationship to motherhood to the idea of 'free-choice eugenics', Jean-Hugues Déchaux looks back over the ethical controversies surrounding genetic engineering.

Since the Mendelian laws of inheritance were rediscovered over a century ago and since the double helix structure of DNA was determined in 1953, genetics has become the reining discipline in the life sciences (Morange, 2017). Biological knowledge has seen considerable progress, drawing in part on advances in physics, chemistry, and computer science. Genetic engineering, which consists in modifying the genome of an organism by manipulating its DNA, took off from the 1970s onwards. In medicine, so-called 'gene' therapies emerged, aimed at targeting the gene(s) behind the disease, while extraordinarily precise screening and diagnostic tools were developed. Today, genetics is increasingly used in reproductive medicine and this has changed not only the technical modalities of medical supervision of pregnancy but also, more profoundly and imperceptibly, representations of human reproduction. Our former points of reference in terms of life, the body, illness, and childbirth have all been shaken. Other ways of envisaging birth, reproduction, transmission, and therefore parenthood, to some extent, are emerging generating debate and controversy.

The antenatal

By trying to determine the precise relationship between genes and proteins, through the notion of genetic code, molecular biology has transformed perceptions of the living. In 2003, after a long decade of research, this led to the first full reading or 'sequencing' of the human genome. Sequencing has since become commonplace: thanks to bioinformatic and biotechnological methods, it can be carried out quickly and conveniently, particularly for coding DNA (the exome) and at ever decreasing cost. This explains the increase in genetic tests and contributes to promoting a new form of medicine, which is both predictive and personalised, based on analysis of patients' genomes. This has already had concrete effects in obstetrics and these are likely to increase in the coming years. The medical supervision of pregnancy, which previously relied on biochemical and ultrasound screening, now increasingly draws on genetics too: non-invasive prenatal testing (NIPT) requiring only a blood or saliva sample from the pregnant woman gives access to the foetus's DNA from a very early stage (12 weeks post amenorrhea). Many are freely available for sale on the Internet. This has increased the possibility of detecting the risk of having a child with a debilitating or more or less rapidly life-threatening genetic disease. Preconception tests also exist, especially in the United States and in Japan, assessing the risks of hereditary conditions before conception itself.[1] These tests cover a large range of mutations associated with disease and calculate the future parents' genetic compatibility. In Belgium, the Superior Health Council recommends offering and funding these types of tests for all future parents receiving treatment for fertility problems or who have been diagnosed as carriers of a recessive genetic illness. The identification of risk has shifted from the foetus to the parents, before any intended pregnancy has even begun.

Since the creation of a new molecular tool (CRISPR-Cas9) in 2002, targeted alterations can now easily be made to the genome of living organisms. This operation known as 'genome editing' replaces damaged DNA sequences with 'normal' sequences by cutting DNA strands at specific points. International research in this field is flourishing and striving to improve the precision and reliability of genome editing by reducing the risk of unintended collateral changes. For example, a molecular tool developed at the end of 2017, the ABE (Adenine Base Editor), allows the genome to be rewritten 'to the letter' without cutting DNA. While genome editing has not yet been

[1] From the 1970s onwards, certain countries and regions (Cyprus, Greece, Sardinia, etc.) affected by hereditary haemoglobin diseases (sickle cell disease and thalassemias) have organised systematic screening of carriers, forcing couples to take a test before conception.

fully mastered, continuous progress is being made. Its clinical applications in human medicine are beginning to appear in anti-cancer treatments. They consist in editing the patient's somatic cells causing the illness. However, it is also possible to alter the genome of the germ cells concerning reproduction (gametes, embryos at zygote stage).[2] When alterations are made to the germline genome rather than the somatic genome, they are passed down to descendants. This equates to intentionally changing human genetic heritage, which raises vast ethical questions. For this reason, clinical trials on human embryos remain rare and controversial and, thus far, have not aimed to produce children. However, such rapid progress has been made since the inception of CRISPR-Cas9 that technical impediments to germline editing may be overcome sooner than anticipated. Many geneticists are calling for further research and experiments so as better to prevent inheritable recessive diseases (Déchaux, 2007).

The period before birth is becoming a crucial phase during which genetics provides knowledge allowing us to predict more or less accurately the future health of a child or of the adult that child might become. The information provided is statistical in nature: the calculations concern the probability of a disease arising due to genetic damage which, strictly speaking, does not equate to an individual prognosis.[3] With germline editing comes the prospect of a new stage: the possibility of preventing the transmission of genetic diseases that might occur during the life span of an individual or his or her descendants by correcting the mutations responsible. The idea that the reproductive process, from conception to birth, might one day no longer be a lottery but instead be fully controlled is progressively gaining ground. This scenario of possible reproduction without uncertainty has changed the way birth is viewed: it is no longer an event that happens to us but an action undertaken and we seek to control its expected consequences as early as possible (Dumitru, 2003). This rationalisation of reproduction, in the sense of reducing uncertainty, is the logical follow-up to the medical supervision of human reproduction.

[2] A zygote is the fusion of two gametes and the first stage of development after fertilisation.

[3] These are 'relative risks': the risk for the person tested is calculated based on the risk for the general population. A 50% risk therefore does not mean the same thing when the risk of having a particular pathology in the general population is, for example, 0.2% of 10%.

Reproductive choice

When procreating is viewed as making a reproductive choice and trying to control its predictable outcomes, prenatal selection using the biotechnological procedures that reproductive medicine affords future parents takes on crucial importance. Of course, reproductive selection has existed in all human societies to varying degrees, either directly through infanticide and abandonment of children or indirectly through prohibitions concerning marriage between blood relations. However, for the first time in history, the moment of selection has shifted from the postnatal to the antenatal. Reproductive choices are now medically managed: thanks to sequencing, genetic risks can be taken into account and soon it will also be possible to carry out targeted corrections of the embryo's genome. While these choices remain the couple's, they are now genetically assisted and reliant on medical expertise, which, depending on test results, will offer a choice between different scenarios.

At present, whether in terms of traditional screening (ultrasound and biochemical) or non-invasive prenatal tests (NIPT), reproductive selection only operates in the negative: according to the results, a couple can decide not to go through with a pregnancy. However, pre-implantation diagnosis (PGD) coupled with IVF (in certain rare contexts of a particular serious family or personal history) and, in the near future, germline editing, bring the possibility of another rationale: positive selection, in which the parents' choice focuses on the best genome configuration, either by choosing between several available embryos (in the case of PGD) or by directly altering the future child's genetic make-up (with germline editing). Large-scale embryo selection is also within the realm of possibility: from the point at which we have mastered lab production of artificial gametes based on simple skin cells (which genetics can already do for mice), couples could potentially sequence the genomes of a large number of embryos created by in-vitro fertilisation and then choose between them based on the most information possible.

Assisted by medicine and genetic counselling, parents will be placed in a situation where they have to choose a genotype for their unborn child. This new parental prerogative comes with unprecedented responsibility. What reasons and aims should underpin this choice? Various questions abound: with what aim should they choose one genotype rather than another? What is a pathology? What is a normal child? What is a good parent in this regard? Genetics has no scientific answer to give to these questions because the problem is not biological and cannot be resolved by a probabilistic calculation measuring predispositions based on exome sequencing. How

can we distinguish between what is normal and what is not? The answer might seem self-evident in the case of a genetic mutation associated with high risk of incurable cancer, but it is already much less so when it comes to deafness or dwarfism, for example, let alone choice of sex. Parents and doctors are stepping into a realm where the issues at stake no longer relate to biological facts but instead to the preferences and norms that justify assessments and decisions. Reproductive choice explicitly raises the problem of the right reasons for bringing a child into the world. At the antenatal stage of the reproductive process, the important considerations are preferences, beliefs, and ways of envisaging reproduction, parental responsibility, and parenthood.

Reproductive utilitarianism

Arguments in favour of expanding antenatal selection tend systematically to foreground its therapeutic and preventive aims, as evidenced by discussions about the potential applications of germline editing in humans. The key argument used is the gain in human lives. By excluding the genetic mutations that cause incurable diseases, editing would allow many people to live in good conditions or simply not to die: it is about reducing suffering and death. Viewed in these terms, it seems derisory, or so the argument goes, to consider that the human genome is inviolable and should not be intentionally corrected.

For example, in the December 2, 2015 edition of *The Guardian*, Cambridge professor and bioethicist John Harris argued it was absurd to consider the genome inviolable, refuting the most common objections raised, i.e. that it causes an unacceptable risk to future generations because changes in germline affect generations down the line and that it is impossible to obtain the child's consent. In his view, the real tragedy is that 6% of babies born every year in the world carry serious genetic mutations. He argues that germline intervention is not only legitimate, it is also a moral obligation to save human lives. He is not alone in defending this position, certainly in the Anglo-American world. In the August 1, 2015 edition of the *Boston Globe*, Harvard professor of cognitive neuroscience Steven Pinker outlined the range of tragedies that editing human genomes might massively reduce. In 2010, the WHO estimated at 2.5 billion the number of years of human life lost to death or compromised by disability due to disease: far more than all the mass crimes, wars, and genocides in the world. For Pinker, the conclusion is clear: there is a moral imperative to do what must be done to lower the number of years lost.

These arguments are based on a sort of reproductive utilitarianism: correcting the germline genome and, by extension, genetically assisted antenatal selection are a good thing because they fight death and allow gains in human lives. This argument does not distinguish between the collective and the individual. What is good on a collective level, and can be measured in number of years gained without disability, is also good on an individual level for parents concerned about their child's happiness. Protecting that child from a serious genetically transmitted disease by modifying the embryo's genotype is viewed as the parent's moral duty to offer that child the best possible life. The same reasoning could be applied to phenotype (height, sex, IQ, etc.) should the parents consider, rightfully or wrongfully, that a particular feature would make their future child happier. When gains are no longer measured in terms of life expectancy, Harris believes that parents will want the right thing for their offspring because they want them to be happy and that they should therefore be trusted and allowed to judge and decide for themselves, according to their own values (it is up to them to define what constitutes a 'good life'). In this sense, improving a child's physical or cognitive capacities is not very different from the educational choices that parents make very early on in their child's life and in his or her interest. In principle, therefore, there is nothing opposing the use of germline genome editing for enhancement purposes. Certain geneticists share this point of view and underscore the need for the most reliable editing tools possible. In the April 10, 2016 edition of the *Wall Street Journal,* geneticist George Church stated:

> For gene editing, we can focus initially on fixing the most deadly, currently incurable genetic diseases in newborns. If these editing therapies are safe and effective, then we can move on to targeting other traits.

Free-choice eugenics

This quest for improvement can also be seen in a well-established intellectual trend in Anglo-American countries, which aligns itself with eugenics and human enhancement. The highly technical debate about germline genome editing has also marked the return of eugenics – understood as conscious and voluntary reproductive selection with a view to improving human genetic heritage – as a societal issue, in its novel 'free-choice' iteration.

Historically, eugenics took the shape of a public policy aimed at selecting parents in a more or less authoritarian fashion by excluding individuals considered

'degenerate'. This was a state eugenics. From the 1920s and until the Second World War, several Western countries adopted eugenics legislation (some states in the USA, Switzerland, Canada, the Scandinavian countries, Nazi Germany). With free-choice eugenics, parental requests replace state constraints. To take up Thomas C. Schelling's visionary expression, it is a question of 'choosing *our own* children's genes' (Schelling 2006 [1978], p. 193). Over recent decades, eugenics has become a taboo, inevitably associated with the Nazi experience. This phobia therefore had to be transformed into a positive term embodying a legitimate option and this conversion was made possible by the notion of 'free choice'.

In the Anglo-American world (Australia, Canada, the United States, and the United Kingdom), theorists of this new eugenics express their views in the world's most prestigious academic institutions, as well as in the media. Two key examples can be cited. The first is philosopher Nicholas Agar, professor at Victoria University of Wellington, who published the founding text of this doctrine entitled 'Liberal Eugenics' in 1998 in the US journal *Public Affairs Quarterly* and then developed his ideas in a book in 2004, sporting the explicit subtitle: 'In Defence of Human Enhancement'. Agar defends a liberal version of eugenics giving parents the right to modify their future child's DNA. He sees this parental eugenics as a sign of democracy, the expression and extension of a reproductive freedom that, in his view – and provided equal access is ensured to reproductive biotechnologies – can function as a tool allowing equal opportunities and abilities.

Julien Savulescu, a philosopher specialising in bioethics at the University of Oxford, is highly influential in academic circles regarding the issue of reproductive selection. In the early 2000s, on the subject of PGD, he introduced the notion of 'procreative beneficience': parents have the moral obligation to select the best genes for their children with a view to providing them with the best life possible, based on the information at their disposal. This text, published in the journal *Bioethics* in 2001, can be seen as the manifesto for new eugenics and, year after year, continues to be a reference for advocates of antenatal selection. Whether alone or with members of his team, Savulescu regularly takes a stand on research in procreative genetics – regarding CRISPR-Cas9, for example, but also the creation of artificial gametes or births achieved by mitochondrial replacement techniques, inaccurately dubbed 'three-parent IVF'[4] – when he believes they offer greater control over individual genetic fate. The

[4] This technique consists in replacing the mitochondrion carrying mutations in a non-fertilised egg or in the embryo (at zygote stage) with mitochondrion from a woman who is not a carrier of these mutations. Mitochondrion, which produce energy in cells, are passed on by the mother.

therapeutic or preventive argument justifies continually moving forward the point at which selection should take place.

Within this new eugenics, the state's role is simply to make it possible for parents to exercise their freedom of choice. This argument is predominantly based on a conception of responsibility for others – the corollary of free choice – that is assessed in utilitarian terms.[5] Potential options are ranked according to anticipated consequences: How much less risk of pathologies? How much less suffering and how many fewer deaths? How can the 'best life possible' be ensured for the child? The repeated use of the word 'best' – best child, best life, best advantages – illustrates this utilitarianism which concludes that the duty of selection is the best choice possible and therefore frames itself as altruistic. What this new eugenics has in common with its state version is a focus on genetics viewed from a deterministic perspective that emphasises the importance of heredity and downplays or even ignores the importance of environment. However, the two are embedded in very different intellectual worlds. The new eugenics has divested itself of notions of the degeneration of the human race and focuses instead on the individual, on reproductive choice, on rational decision-making, and on parents' moral responsibility. It presents the notion of a genetically responsible parent who has a duty to choose between good and bad genes.

The ethical controversy

At the heart of discussions about antenatal selection and its remit and tools lies the sensitive issue of the distinction between treatment and enhancement aims, sometimes translated into a somewhat exaggerated opposition between immediately acceptable medical uses and unacceptable cosmetic uses. Defences foreground the therapeutic (or preventive) argument, while hostile perspectives point to the risks of using selection for enhancement purposes without the guidance of therapeutic aims and with a view to improving the child's physical or cognitive capacities. This controversy reveals an ethical opposition relating to contrasting premises.

The moral utilitarianism justifying broad use of antenatal selection, and particularly genome editing, that prevails in Anglo-American bioethical reflections

[5] While Agar's stated allegiance is to individual freedom, Savulescu, Harris, and Pinker reason in utilitarian terms, which leads to different points of view on germline editing where Agar is more circumspect.

does not draw a clear distinction between treatment and enhancement aims. Its founding concepts – individual freedom and autonomy, free choice, interest, anticipating consequences according to a calculation for maximising utility – do not allow for this distinction because the question of aims (the intended utility) is left to the judgment of the parent(s), who are assumed to want the best for their child. At stake is individuals being able to choose what is best for them, or more specifically for their child. Gains in life expectancy without disability (on an individual scale) or in number of human lives (on a collective scale) offer a simple measure of the best life possible, often used by proponents of antenatal selection. However, while it may be simple, it is not the only way of defining what is 'best'. Depending on parental preferences, beliefs, and convictions, offering their child the best life possible could also mean allowing that child to be male rather than female, to be taller, to have fairer skin, to be more intelligent, etc. If, by therapeutic aims, we mean obtaining a better life for a child, it is hard to determine the boundaries of what falls under this remit and this paves the way for enhancement, or at the very least, does not, in principle, preclude it. In this sense, free-choice eugenics can therefore be considered similar to transhumanist stances which recommend using biotechnology and reproductive medicine to enhance the human race, if only to fight against the natural inequalities that result from the genetic lottery (Savulescu and Bostrom, 2011).

The alternative consists in thinking in terms of human dignity. This brings the question of intention back into ethical reasoning, asking whether or not the aims are compatible with human dignity. The heart of the controversy lies in the contrast between Anglo-American moral utilitarianism and a more continental tradition that draws on this notion of human dignity. In the United States and the United Kingdom, many authors contend that the very idea of 'human dignity' is devoid of meaning (Macklin, 2003; Cochrane, 2010): they argue it is a metaphysical illusion that resists definition and is contrary to the evolutionary nature of human life and the human condition. Conversely, its proponents believe that this notion alone can allow for true equality between human beings and avoid asymmetrical situations where one individual (the parent) could decide the genotype of another (the unborn child) before the latter even exists (Habermas, 2003). In a similar vein, life can also be considered as something we do not have the right to control, something that is 'given', in the true sense of the word, if only by chance, and that being free means adapting to this rather than denying it (Sandel, 2007). Finally, the notion of dignity is also said to present the advantage of conceiving of humans in their social relations more than individualist approaches based on principles of autonomy and interest (De Melo-Martin, 2012).

This ethical controversy is echoed in institutional stances. It inspires the positions of official bodies, particularly regarding the strongly debated issue of germline therapy. The most hostile positions – taken, for example, by UNESCO in 2015 and the Council of Europe in the Oviedo Convention (1997) and more recently in the Parliament's Recommendation of October 12, 2017 – conclude that the human genome is inviolable in the name of human dignity. Conversely, regulatory bodies in Britain (decision by the Human Fertilisation and Embryology Authority in February 2016; Nuffield Council report on Bioethics in September 2016) and the United States (National Academy of Science report, February 2017) come closer to a utilitarian ethics of individual freedom and are not opposed to the idea of clinical applications of germline editing in humans once the tools have proved reliable.

Genocentrism and genetic marketing

The debate surrounding antenatal selection, revived or generated by advances in genomics, stands against a backdrop of astoundingly resistant simplistic and deterministic views of genetics. Most of the people crafting and opposing germline editing share the same 'genocentric' view of human beings: in one case, this justifies providing the means to replace damaged DNA sequences with 'normal' ones, and doing so in the germline so as definitely to eradicate life-threatening or debilitating diseases or provide unborn children with a better genetic make-up; in the other, it justifies, on the contrary, the idea that human genetic heritage is inviolable on the basis that intentionally changing genes means deciding the life an individual will have and therefore making people into products that can be 'tailor-made'. Both contrasting positions implicitly accept the postulate that everything making up human beings, and even their value, is entirely encoded in the genome. This observation recalls the point made by Dorothy Nelkin and Susan Lindee several years ago now (Nelkin and Lindee, 1995): after investigating representations of genetics in North American popular culture, these sociologists concluded that there a 'DNA mystique' existed.

For a while, this essentialist determinism was also characteristic of research, when the geneticists involved in the Human Genome Project (1990-2003) believed that sequencing the whole genome would allow them to read 'the Book of Life' (to use British researcher John Sulston's expression). In reality, the biological processes relating to genetic investigation proved far more complex than this reductive, if not simplistic, image of genetic code. Advances revealed multi-facetted and imbricated

interactions at the level of the genome, which is now studied as a network or a system. Researchers have a better sense of the varied epigenetic impact of environmental or behavioural factors. In most cases, genetics shows there is no linear causal link between a given genetic mutation and a given pathology. Where this causality does exist, it only concerns a small number of mutations and diseases. The more research advances, the more the relationship between genotype and phenotype proves complex, an epistemological shift that some argue marks the beginning of the 'postgenomic' (Perbal, 2011; Reardon, 2017).

How can the persistence of this genocentrism be explained? The marketing of genetics is a crucial factor here, although its importance is all too often downplayed despite its massive scale in recent years. Many renowned researchers, such as the inventors of CRISPR-Cas9, have also created businesses and start-ups and have signed agreements with major pharmaceutical or biotechnology companies. The market for gametes, genetic tests, sequencing, biogenetic big data, predictive and personalised medicine, etc. is also important in this regard. The financial stakes are colossal both for biological economics (and this includes the digital giants) and for the governments of countries engaged in extremely acute international competition. The result is that scientific and economic rationales are increasingly imbricated, while also being affected by normative stances concerning individual rights (the right to know one's DNA or that of one's biological parent, the right to sell one's own biogenetic data, etc.), medically assisted reproduction, and research on embryos – issues which are all subject to regular changes in legislation. Individuals and institutions at the intersection of these different rationales take public stances on the matter. At the heart of these controversies about antenatal selection, whether revived or generated by scientific progress, lies the marketing of genes which contributes to maintaining, and perhaps even to enhancing, the DNA mystique. It is as though genetics were ever more torn between scientific knowledge, attentive to complexity, and a widespread reductive creed – sometimes even adopted by geneticists themselves – conveying economic interests and ideological issues relating to the definition and status of the living.

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