Opinion

How Much Is Too Much?
Concerns About Trivializing Biomedical Interventions From Conception To Death

A Concerned MD, PhD

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For some time now, certainly since the global deployment of mRNA technology in the name of vaccination, I have been wondering where bioethicists (along with common sense) have gone. I have three hypotheses: the first one is that many ethicists lack the training to raise certain questions. This is not their fault for most biomedical scientists and bioethicists may be operating under the premise (which may be false) that all technological advances (and the choice of the word "advancement" may be at the heart of the misconception) have an inherent component of betterment. Consequently, they have probably not even asked whether the overall risk-benefit ratio of new applications of biotechnology favors humanity. The second one is that many of them are intimidated and therefore pushed into silence due to the huge influence of the biomedical/biotechnology industrial complex over the ruling class (our governments and stakeholders). Not only do industry and governments have deep pockets to fund the best marketing campaigns, they also often provide most of the direct funding to support the activities of academics engaged in biomedical ethics research. The main marketing message is that new biomedical molecular and cellular technologies (that modify normal and natural cell functions) are safe and effective and are here to stay because they will solve all health problems, either acute or chronic (*e.g.,* prevention of infections, cancers, autoimmune diseases, metabolic diseases, etc.), and they will also "improve" the aging process. My third hypothesis is more chilling, because it implies that most or all biomedical scientists and bioethicists agree with the global use of these revolutionary technologies, as if it was an inevitable continuum of human enterprise…but is this even possible?

I hope not, because the public should be aware of diverse perspectives on this vital subject.

I am not an ethicist, so this is not meant to be an expert ethical analysis. It does not, therefore, provide an analysis through the lens of one or more of the main ethical theories (consequentialism, deontology, virtue-ethics, *etc.*). I am also not a religious person, so my focus will not be on the theological dimensions and implications of these issues. I am just a concerned MD. PhD., who has been working in biomedical research for almost twenty years, and who wonders what has happened to the notion of respect for nature, specifically human nature

Why do I say that something has affected the respect for human nature in particular? Because, paradoxically, our modern Western societies have acquired a high level of concern about not disrupting any of the non-human species around us. We are extremely worried when human activities pollute and destroy wild animal species and their environments, and we want our green spaces to be restored, preserved, and thriving. Our governments invest in the preservation of natural spaces, and they ban human activity that could potentially change the environment or ecosystem. This is all commendable. However, we do not seem to have any problem (nor ethical qualm) about interfering with our own human biology and the normal biological functioning of

human cells underlying our human nature. Thus, the global use of new cellular/molecular biomedical technologies, such as in cell translation of lab-manufactured mRNA into novel proteins, that modify basic, central, and normal functions of human cells, not because these cells are defective or sick, but simply to improve or add a new functionality, should be a subject of deep societal concern or at least interest.

So, in this essay, I will present my thoughts, concerns, and unanswered questions about some of the technologies that we are developing and using in the biomedical research field, which are already affecting our human nature, and which may affect it even more profoundly in the future.

What happened on a global scale during the COVID-19 crisis took me by surprise, because one of the technologies that was favored to try to prevent an infectious disease was that of a modified mRNA created in a lab, to make our humans cells carry out a function that they would normally never perform. There are many downsides that have been described by scientists who are critical of mRNA technology, such as the impossibility to measure the quantity and quality of the proteins translated under the command of lab-manufactured mRNA; this constitutes a breach of the pharmacologic principle of precise dose of the active pharmacologic product (in this case, the protein translated). Remember the famous dictum attributed to the 16th Century German-Swiss physician and alchemist Paracelsus, "*What is there that is not poison? All things are poison and nothing is without poison. Solely the dose determines that a thing is not a poison."* Also, it is impossible to ensure in which cells that translation happens, since these mRNAs are transported in lipid nanoparticles that have the capability of entering any cell and travel everywhere. Their distribution in the body depends on how many of them can go from the interstitial space (space between the cells) where they are administered by intramuscular injection to the lymphatic and venous systems (since there is no guarantee that 100% of them will be cleared by the lymphatic nodes) to the heart and the arterial system for distribution to all the organs in the body. This breaches the second most important principle of pharmacology, that of precise knowledge of the biodistribution of a pharmacologic product.

These criticisms are valid and important, but most intriguing to me as a physician were not only the formal pharmacokinetic and pharmacodynamic liabilities of mRNA, but the simple fact that we were changing the normal function of cells that were not sick or abnormal by any known criteria or definition. Why turn healthy human cells into factories to produce a protein that is foreign in nature? Why are we interested in giving to our cells new alien capabilities? And why do we assume that doing so will be without consequence? *Is our normal natural functioning defective or inadequate?* Or is it the defect in our reasoning?

Once this question appeared in my mind, I started thinking about other medical interventions that have resulted from biomedical research, not only to cure diseases or anomalous deficits (both of which could cause suffering and maybe the premature death of people, so instinctively and compassionately we lean towards solving those issues without complex ethical considerations), but to simply change the normal natural function because we consider that it would be better that way, implying that the normal natural function is in itself insufficient or defective. And when I decided to list these interventions that modify normal function, I realized that many (maybe most of them) are used in key stages of our natural life cycle. These stages include: 1) conception; 2) *in utero* development; 3) birth; 4) growth and sexual/reproductive maturation; 5) reproduction; 6) advanced aging; and 7) death. All these fundamental milestones in human development are characterised by changes in cellular number and function and are genetically programmed to happen in a particular sequence. We do not know exactly why certain milestones happen at a certain age and not later, but apparently, we believe we know that the natural order and timing may be improved by our intellectual endeavours and translated into technological inventions that allow the manipulation of normal biological functions.

Thus, in chronological order, let us consider the interventions that modify the beginning: conception, *in utero* development, and birth. For a long time now, humans have had the possibility to control birth, by either preventing conception (*i.e.*, all contraceptive methods, including surgical ones, such as vasectomies and tubal ligation), preventing or stopping the development of the embryo/fetus (*i.e.*, pharmacologically -day after pill- or mechanically -abortion), or allowing conception using pharmacological stimulation (*i.e.*, induced ovulation), laboratory assisted combination of eggs and sperm (*i.e.*, *in vitro* fertilization (IVF)), the development of the embryo in a womb different from the mother (*i.e.*, surrogacy), and most recently (still in the research phase to be used in humans) the development of artificial wombs to keep very premature fetuses developing outside the maternal body when there is an abnormal, very premature delivery. Many of these interventions are used not because we are sick, but because we want to determine when conception and birth will happen, we want to decide the time that is most appropriate for us, according to the situation that we are living, not necessarily because we have a health problem (although, of course, they are also used when there is a health problem). Moreover, we must consider that some of these technologies came about to enable conception and birth beyond a certain age. So, for better or for worse, we now can decide *if* and *when* life begins.

After being born, we grow and mature into reproductively active beings, which means that we go through puberty, maturing sexually. This stage has recently been revolutionized by hormonal pharmacologic interventions that allow the delay of puberty and the change of the hormonal profile genetically determined in an attempt to change sex/gender. These hormonal treatments

change some phenotypical characteristics of the person (*e.g.,* deepen the voice pitch of genetical females), so the only avenue to complete the transformation is surgical, by removing natural and normal functioning organs (*e.g*., breasts, or penis), and creating *de novo* organs that do not develop naturally (*e.g*., neo-vagina, or neo-penis). These interventions are not performed to cure any disease, since puberty is not a sickness of the genitourinary/reproductive system, they are done to enforce the will of the individual who believes, or somehow perceives, that their natural genetic pathway of development is wrong. Moreover, even when the long-term consequences of these interventions have not been assessed, several secondary effects of the hormonal and surgical therapies have been described. But these negative consequences (including infertility), which may cause physical harm and disease, are downplayed as irrelevant, since the most important goal is the fulfillment of the will of the person who wants to transform into a sex different from their genetic identity. It is also worth noting that these interventions will remain superficial, even if they appear to be physically profound, because every cell of the body retains a chromosomal difference (*i.e*., XX or XY chromosomes) that defines their cellular functions, which have evolved after over a billion years of sexual reproduction (*e.g*., production of given amounts of specific hormones). But, for better or for worse, we can decide *how* we grow and *into what* we mature.

Once we reach the mature stage, and we are adults, most of us will have the capacity to reproduce within the time span when the functionality of the reproductive system is at its peak. This optimal window is shorter, ending at an earlier age, for women than for men, and it is usually lost in trans-individuals who undergo radical genital surgery. In addition, very often in Western modern societies, the optimal window of reproduction in women is occupied by other activities (*e.g*., pursuing higher education and a career), making reproduction not ideal at that time, and pushing it to a later age, when the optimal reproductive functionality decreases. Of course, this is now considered not so problematic, because we have technological interventions (now defined as treatments, because they aim to recapture a function -reproduction- that is not taking place) that allow pregnancy much later in life (*e.g.*, IVF), or in the womb of another woman (*i.e*., surrogacy), and we still do not know how the technology of artificial wombs will evolve, since what researchers claim as treatment for very-premature fetuses who would never survive without a womb-like environment, could easily evolve to the complete development of embryos and fetuses in artificial wombs, outside the maternal body altogether. It is interesting to note that because of social/cultural changes that allow women to study and work in areas that were unthinkable a few decades ago, we have brought about biomedical interventions on reproductive events that should normally happen during the optimal window of time determined by our natural biology. Instead of trying to intervene or modify the social aspects (*e.g*., organising systems that allow women to have children when they are younger, and completing their studies

and developing their careers after the children are born), we have preferred to intervene in the normal biological and chronological functions. Is this because biological interventions are easier than social/cultural changes? Or is it because our intellect conceives that the timing decided by our will and our culture is more correct than what biology offers? Interestingly, this biology-intervention approach may come at a price for the next generation, because the longer that women delay having children, the greater chance they have of accumulating mutations in their stored oocyte precursors of eggs. This in turn might affect their babies who may end up being predisposed to developmental ailments, and/or other diseases where genetics plays a significant role. So, for better or for worse, we can now decide *when* we reproduce, which is a synonym of determining *when* life begins for the next generation.

Then, once we have reproduced, we continue to age, and with the aging process comes along the more or less pronounced decline in function of our organs and systems and the potential development of chronic ailments. In women, the functional decline of the reproductive system, which entails the depletion of the source of eggs, with the consequent decline in the possibility of pregnancy, is marked by hormonal changes that bring about a series of symptoms known as menopause. These changes are natural, however, we offer hormonal treatment to reduce the symptoms, as if they were part of a disease. But is menopause a disease?

Also, as both women and men age, they may develop metabolic, cardiovascular, cerebrovascular, and cognitive problems, some with specific disease diagnosis, some not. Many of these problems are immensely ameliorated, and sometimes completely disappear, by changes in lifestyle through diet, exercise, social connections, and stress reduction. However, because changing habits is a difficult task, we lean on pharmaceutical and biomedical technologies, which could somehow offset or revert the chronic problems and the normal aging decline. But is aging a disease? Do we need to cure aging? Are we not under the guise of improving the quality of life, trying to outsmart biology? We are now in possession of technology that can change or add functions to the cells, so if normal aging muscle cells decline in function reducing the amount of fibrillary proteins that they produce, with the consequent muscle mass decline and increased weakness of the locomotor system (one of the reasons why older people are prone to falling when they walk), should we via mRNA or other gene technology increase productions of those proteins? The same logic may apply to joints and cartilage. Should we keep cartilage vital via these new technologies that manipulate/increase protein synthesis inside our cells, so the degenerative arthritic process is stopped or delayed? Is the ultimate goal to keep cells in a constant stage of youth? There are biomedical companies that claim that gene therapies and stem cells therapies are the natural continuum of holistic and natural health supplementation approaches, designed to improve the quality of life and make us live longer, up to 120 years old.

Our intellect has created biotechnology apparently superior to natural biological processes. So, for better or for worse, we aim to decide *how* and *when* we get old.

Finally, when we reach the end of the life cycle, we all die. But when and how that happens has also been revolutionized lately. Many countries in the Western world have legally allowed medical assistance in dying (MAID) as a form of last treatment to a person suffering from a terminal disease (*i.e.*, when there is a 100% certainty of death as the outcome). So, the reduction of pointless suffering is seen as beneficial to a patient who does not have any chance of natural survival. Unfortunately, this very restricted use of MAID is experiencing considerably expansion and may be applied in the future to people suffering from mental health problems, or chronic pain, or motor disabilities, which are not terminal health problems, but ailments that pose a series of challenges and inconveniences that could be ameliorated with interventions of different types. So, for better or for worse, we can decide *when* we die –with the help of the state.

In the light of all of these interventions and technologies modifying normal functions that supposedly improve our human nature, the questions that I have are:

1) How can we be sure that the change in question is an actual improvement, that it is somehow better or more beneficial than the previous state of function? What are the criteria for, or definition of "improvement"?

2) Have all potential adverse effects of these technologies been determined in the short, medium, and long-term? And is it even possible to precisely pinpoint all those effects, especially long-term adverse effects, given the biological complexity of human individuals and the immense number of uncontrolled covariables that could affect the outcome of interest? Moreover, do we have all the necessary information and the foresight to assess and/or infer all potential (anticipated and not anticipated) consequences of the new technologies?

3) Many (maybe all) of these technologies have initially been developed to ameliorate some type of ailment (with or without specific diagnosis) or to diminish suffering. However, with their sustained use, the applications expanded to situations that are not related to ailments or suffering, but with the wish or personal preferences of the consumers. They may potentially be used to augment and enhance functions to provide competitive advantages. Do we think that future technologies will be better applied to specific situations where alleviating suffering is the main concern, or are all technologies that change normal biological functions destined to become utilities of personal consumption at will?

4) What do these technologies do to human nature? Should human intellectual inventions and technologies be in command of these biological changes because we somehow have deemed them as beneficial? Who decides whether such innovations are in the best interest (or produce an objective betterment) of the human species and how should these individuals go about making these judgements?

5) How do we reconcile this spree of human technological modifications with the challenge of preserving the environment, including all forms of wildlife in their natural state? Are we really respecting ecology in the planet if humans are self-changing their own natural functions? In other words, we complain that unchecked human technological activities have had a negative (some say catastrophic and irreversible) impact on our planet and all forms of life, and yet we seem to believe that no negative impact will come to us by altering the key natural stages of the human life cycle.

In short, do we know better than nature? From conception to death, how much intervention is too much intervention? I think these are the vital questions that we should all be asking ourselves.

A concerned MD. PhD.