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GENETIC MODIFICATION OF THE HUMAN GERM LINE: THE REASONS WHY THIS PROJECT HAS FADED

CHANGER LES GENES? UN PROJET QUI N'EST PLUS PRIORITAIRE

Résumé:
La modification ciblée de la lignée germinale (et donc de l'espèce humaine) est restée un objectif distant mais raisonnable, depuis l'émergence de la génétique (et même avant) jusqu'à ces dernières années. J'ai choisi trois temps pour étudier les évolutions historiques de ce projet – dans les années 1930, au sommet du mouvement eugéniste, autour de 1974 quand la biologie moléculaire triomphait, et aujourd'hui – et j'ai sélectionné trois critères pour estimer la faisabilité d'un tel projet – l'état des connaissances scientifiques, l'existence de techniques adaptées, et les demandes de la société. Bien que les techniques longtemps espérées pour modifier la lignée germinale soient aujourd'hui disponibles, je montrerai que la plupart des attentes qui soutenaient ce projet ont disparu, ou sont considérées comme pouvant être atteintes par des stratégies totalement différentes.

Abstract:
Modification of the human germ line has remained a distant but valuable objective for most biologists since the emergence of genetics (and even before). To study the historical transformations of this project, I have selected three periods—the 1930s, at the pinnacle of eugenics, around 1974 when molecular biology triumphed, and today—and have adopted three criteria to estimate the feasibility of this project: the state of scientific knowledge, the existence of suitable tools, and societal demands. Although the long-awaited techniques to modify the germ line are now available, I will show that most of the expectations behind this project have disappeared, or are considered as being reachable by highly different strategies.

Mots clés:
Amélioration de l'être humain; biologie moléculaire; édition du génome; eugénisme; recombinaison homologue

Key words:
Eugenics; genome editing: homologous recombination; human enhancement; molecular biology

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The Colloquium "Biologie et devenir de l'homme" was organized in Paris in 1974, at a time when the new discipline of molecular biology had a very high profile. In the preceding years, the chemical nature and structure of the genes had been unveiled, the origin of mutations understood, and the precise relation between genes and proteins (the genetic code) discovered. Molecular biology had rapidly acquired a dominant position within scientific institutions: the recent appointment of Jacques Monod to Director of the Pasteur Institute was a sign of this newly acquired power. In addition, molecular biology was on the eve of a new revolution—the rise of genetic engineering. The projects were already there, and the first steps had been accomplished in US laboratories. However, these early achievements had been acknowledged by a very small number of French biologists.

The objective of the 1974 Colloquium was to discuss the new powers of biology, and the new duties of biologists. Within this framework, I have decided to examine how the project to modify the human germ line genetically was reconsidered after the rise of molecular biology, and what it has become forty years later, with the huge amount of biological information acquired since the beginnings of molecular biology. This project has a very long historical background, even if the name given to it changed with the state of knowledge, and the tools at its disposal. What would in the past have been called "transformation of the human species" is now considered as "genetic enhancement", or more neutrally as "genome editing". Despite these changes in vocabulary, the objective has remained similar, with its two projects—the correction of genetic defects and the enhancement of human genetic abilities. I will compare these two projects and the contrasting attitudes towards them, in the 1970s and today. I needed a point of reference, which I have chosen as the 1930s, at the pinnacle of eugenics. In the first part, I will present the criteria that I have selected to estimate the feasibility of these projects at a given time. Quite surprisingly, I will provide evidence for an inverse relation between the extent of knowledge and the availability of techniques permitting the modification of the genome, and the priority accorded to these projects. Today, the technologies are there, but the motivation has disappeared!

CRITERIA TO ESTIMATE THE FEASIBILITY OF THESE PROJECTS

Three criteria must be fulfilled for such projects to be developed. The first is a sufficient state of knowledge. The second is the availability of tools permitting their realization. And the third is that such projects have to be considered as valuable, a priority not only for specialists, but for a large fraction of society. These criteria are obviously of relative value. Scientific knowledge can be considered sufficient at a given time, and only later shown to have been insufficient to support the projects that were proposed. The social consensus is never perfect and is particularly difficult to gauge in authoritarian societies. The notion of "scientific knowledge" is not as simple as might be thought at first glance: to appreciate the consequences of a genetic modification of the germ line, the skills of molecular biologists are not sufficient: population geneticists and evolutionary biologists are needed to estimate the long-term consequences of these modifications.

PROJECTS IN THE 1930S

The idea that it was necessary to control (and to improve) human reproduction is not new. Plato, and Cabanis at the beginning of the 19th century, were advocates. After the acceptance of Darwinian evolutionary theory, this ambition dramatically evolved into the idea of replacing the action of natural selection, which had disappeared in human societies because of the development of social and medical care, by artificial selection. It was deemed necessary both to improve the reproduction of the best and to prevent the reproduction of individuals likely to transmit their physical and mental deficiencies to their progeny.

Eugenic methods of forced sterilization were not unanimously accepted in the first decades of the 20th century, but there was a wide consensus on the necessity and possibility to improve the human species. The talk given by the physical chemist Jean Perrin at the inauguration of the newly constructed Institute of Physical-Chemical Biology (IBPC) in Paris in 1927 bears witness to these expectations: "The issue is to modify, maybe to a prodigious degree, the type of equilibrium, the organs, the hereditary basis of organisms. This search for an experimental transformation of species will play for the biologist a role analogous to that played for the chemist for centuries by the transmutation of elements... This research may lead us, must lead us, to transform current human beings, unchanged for millennia, into higher and higher beings, richer in sensations, feelings, and thoughts, and more generally richer in

what will correspond for consciousness to a wider and more complex development of the brain" (1).

The stimulating role of physics in future developments in biology is obvious in this quotation: the transformation of elements has become feasible for the chemist, as the transformation of species will be for the biologist in the near future. Experimental transformism refers to the neo-Lamarckian tradition dominant among French biologists (2), according to which organisms can be directly modified through changes in the environment.

In the following years, under the impetus given by population geneticists, the Modern Synthesis between genetics and Darwinism was elaborated by the evolutionary biologists Julian Huxley, Ernst Mayr, Theodosius Dobzhansky, George Simpson and others. Most of the founders of the Modern Synthesis accepted the idea that human beings were at the top of evolution, the first to have had access to its rules. For this reason, they were now in charge of evolution, of the future transformations of organisms and human beings (3). Even George Simpson, the most committed of evolutionary biologists in the fight against finalism, nevertheless admitted that "the fact that man knows that he evolves entails the possibility that he can do something to influence his own biological destiny" (4).

By using our criterion of feasibility, it is obvious that these projects were beyond reach. The experimental transformism never worked, *i.e.* changes in the environment never directly produced stable modifications of the progeny. The models used by eugenicists to develop their projects were rapidly shown to be not only simplistic, but also scientifically incorrect. Feeble-mindedness, one of the major incentives for forced sterilization, was not due to one unique recessive mutation as initially proposed by H. Goddard (5). And if most of the defects result from recessive mutations, forced sterilization will have a limited effect since it does not prevent the transmission of "bad" copies of the genes through generations.

The consensus in favour of a genetic modification was initially strong, but it progressively faded because of the way the eugenic measures had been applied in the US, and later in Germany. As was argued by Thomas Morgan as early as 1934 in his Nobel lecture, there are other more human ways to address these problems through medicine (6).

PROJECTS AT THE TIME OF THE PARIS CONFERENCE

Molecular biologists had contrasting attitudes towards the projects of gene modification burgeoning in the 1960s and 1970s. Some were enthusiastic. Such was the case of Rollin Hotchkiss, a specialist in bacterial transformation: "The wealthy and other royal families as always can even hope to purchase special advantage, such as determinants of musical ability, linkage groups providing skill in political oratory – or will they prefer skill in such gentlemanly pursuits as polo, or (somewhat less expensive) single factors enabling one to ride graceful and sure on an appropriately well-bred horse?" (7, p.199) Edward Tatum, the discoverer with George Beadle of the one gene–one enzyme relation, with Joshua Lederberg of sexuality in bacteria, was also convinced that with progress in our understanding of functioning and regulation of gene activity, it will be possible "to exclude structural or metabolic errors in the developing organism but also to produce better organisms" (8). Bernard Davis was much more cautious in his "prospects for genetic intervention in man", pointing to the difficulties stemming from the polygenic control of most human traits (9). Jacques Monod was even more pessimistic, considering that the complexity of the genomes of higher organisms prevented their modification, maybe forever (10).

This absence of consensus among scientists reflected the particular situation that prevailed at the end of the 1960s, the contrast between the rapid discovery of the major principles guiding gene action in the preceding period and the complete absence of suitable tools for the isolation and characterization of the genes present in complex organisms. These tools were developed in the 1970s and by the 1980s were widely used in labs.

But there was also no social consensus on the need for such projects. Eugenics has now become a frightening word. Rollin Hotchkiss felt constrained to give credit to the altruism of the exponents of eugenics since the time of Galton – something that has been far from obvious (7, p.197). In the 1960s, in relation to the war in Vietnam, there was a generalized lack of confidence in science and technology.

FROM THE 1970S TO TODAY

In the last forty years, knowledge of genes and of the way they contribute to the construction of organisms and the realization of their functions has progressed dramatically. It has become possible, at least in the most favourable cases, to describe fully the causal chain that relates the product of a gene to the complex functions in the elaboration of which it participates; and to explain, in the case of mutations, the functional modification from the alteration of the gene.

In parallel, Bernard Davis's anticipations have been fully confirmed: in most cases, there is no simple relation between a gene product and a function of the organism. Gene products cooperate in the formation of complex systems. In addition, the actions of genes cannot be understood without a precise description of the hierarchy of the structural levels forming an organism.

What is most remarkable is the technological progress leading to the replacement at will of a gene in a genome by a different, modified version of the gene. As I have mentioned, the first step was the development of genetic engineering in the 1970s. This opened the door to animal and plant transgenesis, and to the first attempts at gene therapy. The main problem was that the position of gene insertion was uncontrolled. It remained impossible to replace a non-functional copy of a gene by a functional one; what was possible was simply to add to the genome a functional copy of the non-functional gene. The insertion might occur close to an oncogene or in a tumour-suppressor gene, facilitating the emergence of tumour cells. This occurred in the first attempts at gene therapy in France at the end of the 1990s in immune deficient babies (the so-called "bubble babies" forced to live in a bubble protecting them from infection) (11).

The only way to target a precise site in the genome was to insert the gene by homologous recombination. This strategy led at the end of the 1980s to the development of the knockout technology permitting the specific inactivation of a gene. The result was achieved not by an increase in the level of homologous recombination, but by the selection of the rare embryonic stem cells in which homologous recombination had occurred (12). These cells were injected into a blastocyst and transgenic animals were obtained at the next generation.

This strategy could obviously not be used for modification of the human germ line. Different methods to increase the proportion of homologous recombination were tried, with results insufficient to permit any application to humans. The breakthrough occurred a few years ago with the adaptation to animals of a system used by bacteria to protect themselves against bacteriophages and foreign plasmids – the CRISPR-Cas system (13). In this system, the action of a nuclease is targeted towards a specific position in the genome by a guiding RNA, in presence of a template for homologous recombination.

The efficiency is now sufficient to permit the correction of a genetic disease such as muscular dystrophy in mice by injection of the three components at the one-cell stage, after fertilization. The percentage of homologous recombination is not yet 100%, but already sufficient to correct the disease (14). It is a completely new result that opens the door to precise editing of the genome.

A second line of research reached the point in its development where a modification in the human germ line seemed not only desirable, but also achievable. The first steps were done by biologists looking for a way to palliate alterations of the cytoplasm in the egg (15). They

showed that the injection of cytoplasmic extracts from normal individuals could correct the cytoplasmic abnormalities. It was hypothesized that these abnormalities probably originated in a dysfunction of mitochondria, and that it was the mitochondria present in the cytoplasmic extracts that corrected the deficiency.

This approach was resumed in the United Kingdom to the point that a therapeutic project was submitted to the Human Fertilisation and Embryology Authority, debated, and approved. Opponents underlined that, using the protocol, this would be the first time a genetic change had been deliberately made to the human germ line (16).

The prospect of deriving sperm cells and eggs from stem cells was also considered to be achievable in the near future (17). This opened the door to the application of the strategy for knocking out genes in animals to genetic modification of the human germ line.

So, in a few years parallel and independent research lines converged, demonstrating the possibility of genetically modifying the human germ line.

Independently, various transgenesis experiments on animals showed that some of these modifications could lead to performance enhancement (18). One of the most emblematic examples was the enhancement of learning and memory obtained by a genetic modification of one receptor of neurotransmitters, the glutamate receptor (19).

In fact, since the 1970s, the hopes expressed by Rollin Hotchkiss and Edward Tatum have never been completely put aside. In 1998, a meeting was organized at the University of California Los Angeles that recommended brushing aside legal obstacles preventing the modification of the human germ line (20). In 2001, Jonathan King described this issue, and the apparently unanimous opposition to these experiments, as “biology’s last taboo” (21).

What might appear as an irreversible move towards modification of the human genome has over recent years had to contend with a growing number of arguments against going in this direction, or suggesting radically different directions to address the same issues.

Some of these arguments are not new. As already argued by Thomas Morgan, some genetic disorders can be addressed using drugs. More recently, Arnold Munnich has strongly argued that it is far too restrictive to limit the fight against genetic diseases to gene therapy. Like many diseases, they could be controlled, or even cured, by well-chosen drugs, and he has afforded examples confirming the efficiency of these indirect strategies (22).

The importance given to the study of epigenetic modifications suggests also that another road—modification of the environment—might be followed to attenuate the effects of gene dysfunction.

Similarly, although it was supported by a very different spirit, the myth of the convergence of nanotechnology, biotechnology, information technology and cognitive science (NBIC) led to radically different ways of enhancing humans, by fitting them with electronic devices to replace the functions of deficient organs. The creation of artificial retinas is progressing rapidly and in a few years will offer new ways to counter the consequences of some genetic defects.

Of the two objectives always sought by supporters of intervention in human reproduction – elimination of defects and enhancement of human abilities – the first may be reached, more simply and efficiently, by early diagnosis (before implantation or prenatally) and elimination of the affected embryos.

For a policy of germline modification to be efficient, it would have to be applied to individuals in whom only one copy of the gene is mutated (heterozygotes). They do not suffer from disease in recessive genetic disorders, which are the most frequent. Therefore, gene editing would create a risk for these individuals, without any direct benefit for them. In addition, a significant proportion of genetic defects are not transmitted by the parents, but arise *de novo* at each generation. The hope to eradicate forever genetic defects in humans is an illusion. Whatever the strategy used, the efforts will have to be permanently reinitiated.

Probably the most significant blow to the vision of a new world in which genome editing would have a major place came from the transformations of evolutionary biology. The idea that humans are at the top of evolution and have the responsibility to prolong its action on themselves and on other organisms has totally disappeared from the writings of evolutionary biologists, and probably also, at least partially, from their thoughts. The idea that mutations are good or bad is simplistic: the effect of a mutation depends upon the environment. A mutation with a deleterious effect can afford a benefit in particular conditions: such is the case for the mutation responsible for sickle cell anaemia which prevents the development of the agent of malaria. It is difficult to predict the short-term effects of a genetic modification – it is often impossible to anticipate its side effects – but it is even more difficult to foresee the long-term effects in future environmental conditions that are unknown.

CONCLUSIONS

There has been a progressive separation between the therapeutic projects of genome editing and the more ambitious projects of genetic enhancement. Some of the former, limited in their objectives, will probably be developed, such as the replacement of mitochondria. Many other issues will find another solution, consisting for instance in earlier and more efficient diagnosis of affected embryos and their elimination.

The place of genetic modification in human enhancement will be limited. Genetic modifications to obtain "superhuman athletes" are still discussed, at least as a possibility that some will try to exploit (24), but it is obvious that this will be a modification of somatic cells in individuals, not of the germ cells. There is no longer any ambition to produce a "race of athletes".

Genetic modification of the germ line would require a consensus on the biological future of mankind that does not exist! A bigger brain is an objective that is no longer considered valuable. And what was sought through the creation of a bigger brain could be achieved by increased interconnection between the human body and electronic devices.

Priorities have changed dramatically since the time when human beings were seen as the masters of evolution. Today, our aim is far less ambitious: to ensure the survival of humans and other species endangered by the uncontrolled human actions of previous centuries!

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