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# Genetic modification of the human germ line: The reasons why this project has no future

## *Changer les gènes ? Un projet qui n'est plus prioritaire*

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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.



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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.



## 1. Introduction

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 as Director of the Pasteur Institute was a sign of this newly acquired power. In addition, molecular biology was on the

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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 of 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!

## 2. 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.

## 3. Projects in the 1930s

The idea that it was necessary to control (and to improve) human reproduction is not new. Plato, as well as Cabanis at the beginning of the 19th century, was an advocate. After the acceptance of the 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