Bioethics and politics - 22 May

1. Benefits and harms of technologies;
2. Crispr and gain of function experiments;
3. Crispr and germ line editing;
4. The locus of medical intervention and social policy.

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1.1 - Benefits and harms of technologies

In Plato's Phaedrus, there is a passage where Socrates recounts the legend of the Egyptian god Theuth giving the writing technology to King Thamus as a gift.

Socrates argues that while writing is supposed to be an aid to memory, it does not make people wiser.

First, it will actually make people forgetful, ceasing to exercises memory.

Moreover, written texts cannot be genuine substitutes to teaching orally, to serious education through argumentative dialogue and critical exchange. After all, writings are "silent".

1.2 - Benefits and harms of technologies

This critical attitude towards technology highlights its harms.

In 19th century England, the “luddites” protested against textile manufacturers adopting machines. This is because the introduction of such machines - like, potentially, any process of automation - increased unemployment and, therefore, social discontent.

In the 1930’s essay “Economic Possibilities for our Grandchildren”, the economist J.M. Keynes predicted this scenario: in 100 years (i.e., 2030), all our economic activities, from agriculture to industry, will be automated so much as to produce “technological unemployment”.

1.3 - Benefits and harms of technologies

But, Keynes also argued, "…. this is only a temporary phase of maladjustment. All this means in the long run that mankind is solving its economic problem."

Unlike Socrates and the Luddites, Keynes seems to be more optimistic about the social effects of technology.

However, Keynes actually saw a different kind of problem: "If the economic problem is solved, mankind will be deprived of its traditional purpose. Will this be a benefit? If one believes at all in the real values of life, the prospect at least opens up the possibility of benefit."

1.4 - Benefits and harms of technologies

Keynes saw, beyond the possibility of benefit, a huge problem with automation.

The problem is: what will we do with our “freedom from pressing economic cares” and extensive free time?

“…. there is no country and no people, I think, who can look forward to the age of leisure and of abundance without a dread. … It is a fearful problem for the ordinary person, with no special talents, to occupy himself, especially if he no longer has roots in the soil or in custom or in the beloved conventions of a traditional society.”

In a sense this is an elitist perspective, but ….

1.5 - Benefits and harms of technologies

…. the point of this preamble is that every technology has potential benefits and harms and that we should carefully evaluate both.

Concerning the harms, issues about the safety of the technology and the social implications of its use are paramount.

The legitimate uses of the technology should be carefully assessed, where this evaluation should take into account a variety of scientific, ethical and political issues.

This is clearly the case with Crispr technologies: what are their legitimate uses? Should we impose a moratorium in some cases? What kind of governance should we seek?

2.1 - Crispr and gain of function experiments

From the start of the Covid pandemic, it was noticed that a lab leak was a possibility.

Did the Wuhan virology lab perform “gain-of-function” experiments on collected bat coronaviruses? In case they did, what kinds of manipulations were performed? And, above all, what kinds of biosafety standards were in place?

It will be very difficult to answer these questions.

Part of the issue is that they were considered illegitimate ones for too long, as this Lancet letter made clear …..

2.2 - Crispr and gain of function experiments

Statement in support of the scientists, public health professionals, and medical professionals of China combatting COVID-19

We are public health scientists who have closely followed the emergence of 2019 novel coronavirus disease (COVID-19) and are deeply concerned about its impact on global health and wellbeing. We have watched as the scientists, public health professionals, and medical professionals of China, in particular, have worked diligently and effectively to rapidly identify the pathogen behind this outbreak, put in place significant measures to reduce its impact, and share their results transparently with the global health community. This effort has been remarkable.

We sign this statement in solidarity with all scientists and health professionals in China who continue to save lives and protect global health during the challenge of the COVID-19 outbreak. We are all in this together, with our Chinese counterparts in the forefront, against this new viral threat.

The rapid, open, and transparent nothing but create fear, rumours, and prejudice that jeopardise our global collaboration in the fight against this virus. We support the call from the Director-General of WHO to promote scientific evidence and unity over misinformation and conjecture.[14] We want you, the science and health professionals of China, to know that we stand with you in your fight against this virus.

We invite others to join us in supporting the scientists, public health professionals, and medical professionals of Wuhan and across China. Stand with our colleagues on the frontline!

We speak in one voice. To add your support for this statement, sign our letter online. LM is editor of ProMED-mail. We declare no competing interests.

Charles Calisher, Dennis Carroll, Rita Colwell, Ronald B Corley, Peter Daszak, Christian Drosten, Luis Enjuanes, Jeremy Farrar, Hume Field, Josie Golding, Alexander Gorbalenya, Bart Haagmans, James M Hughes, William B Karesh, Gerald T Keusch, Sai Kit Lam, Juan Lubroth, John S Mackenzie, Larry Madoff, Jonna Mazet, Peter Palese, Stanley Perlman, Leo Poon, Bernard Roizman, Linda Saif, Kanta Subbarao, Mike Turner

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2.3 - Crispr and gain of function experiments

The Lancet letter states: “The rapid, open, and transparent sharing of data on this outbreak [on the part of China] is now being threatened by rumours and misinformation around its origins. *We stand together to strongly condemn conspiracy theories suggesting that COVID-19 does not have a natural origin*.” [italics added]

To label the lab leak hypothesis a conspiracy theory in the absence of any evidence it had a natural origin was, to put it mildly, controversial.

2.4 - Crispr and gain of function experiments

Had the furin cleavage site being manipulated, possibly with Crispr, in so-called gain-of-function research?

Sars-CoV-2 has a PRRA amino acid sequence at the furin cleavage site. This site is apparently unique to Sars-CoV-2.

This sequence was called “the smoking gun” by David Baltimore, Nobel prize for Physiology and Medicine in 1975 [declaration then somehow retracted].

The “smoking gun” status of this sequence captures its fundamental functional significance because the virus attaches particularly well to human cells; apparently the Sars-CoV-2 furin cleavage site facilitates infection.

2.5 - Crispr and gain of function experiments

Independently of whether Sars-CoV-2 has actually been manipulated in a lab, the big question remains: is gain-of-function research ethically and socially legitimate?

The argument in favour is that, by means of this research, we can predict future pandemics and develop vaccines more quickly. (Note that in the pandemic case vaccines were developed in record time).

(Selgelid M. J. (2016). Gain-of-Function Research: Ethical Analysis. Science and engineering ethics, 22(4), 923–964. https://doi.org/10.1007/s11948-016-9810-1)

2.6 - Crispr and gain of function experiments

The argument against is that gain-of-function research is not needed (as safe research alternatives are available) and that it is too risky, as laboratory accidents might ensue.

The argument against is basically in favour of a moratorium.

In the USA, a moratorium was in place from October 2014 until 19.12.2017, when the US National Institutes of Health (NIH) resumed funding for gain-of-function research on influenza, MERS and severe acute respiratory syndrome coronavirus. (Burki T. (2018). Ban on gain-of-function studies ends. The Lancet. Infectious diseases, 18(2), 148–149. https://doi.org/10.1016/S1473-3099(18)30006-9)

2.7 - Crispr and gain of function experiments

One big issue is that a local moratorium is insufficient to prevent potential consequences at the global level.

One way out of this would be to have an international agency overseeing gain-of-function research.

A precedent is the supervision of smallpox research by the WHO.

How likely we are to find a global agreement on this research is difficult to predict.

It seems to me there are only reasons to be pessimistic.

3.1 - Crispr and human germ line editing

Take again He Jiankui's case.

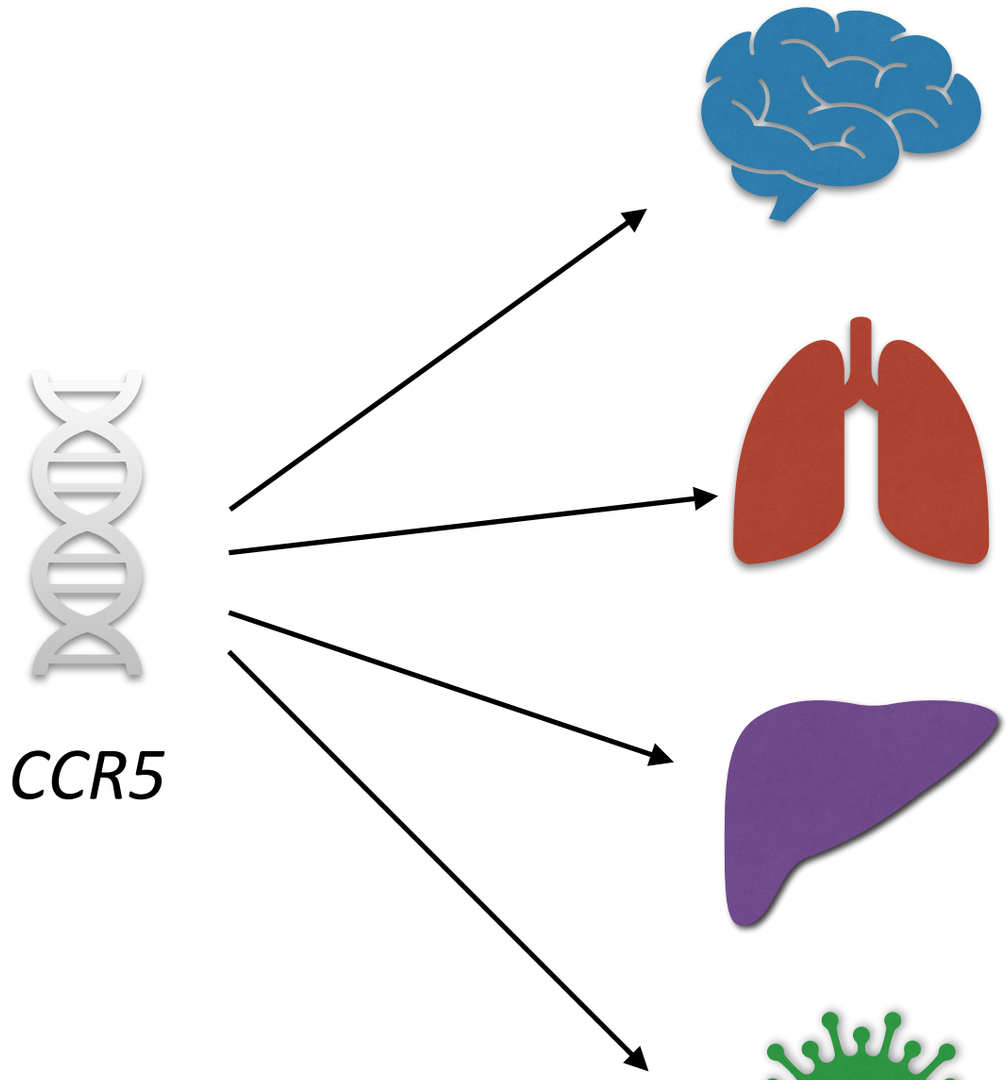
In the last class, I argued (following Sarkar) that the ethical manipulation through Crispr of the human germ line requires strict standards of safety and thorough biological knowledge concerning gene action and interaction:

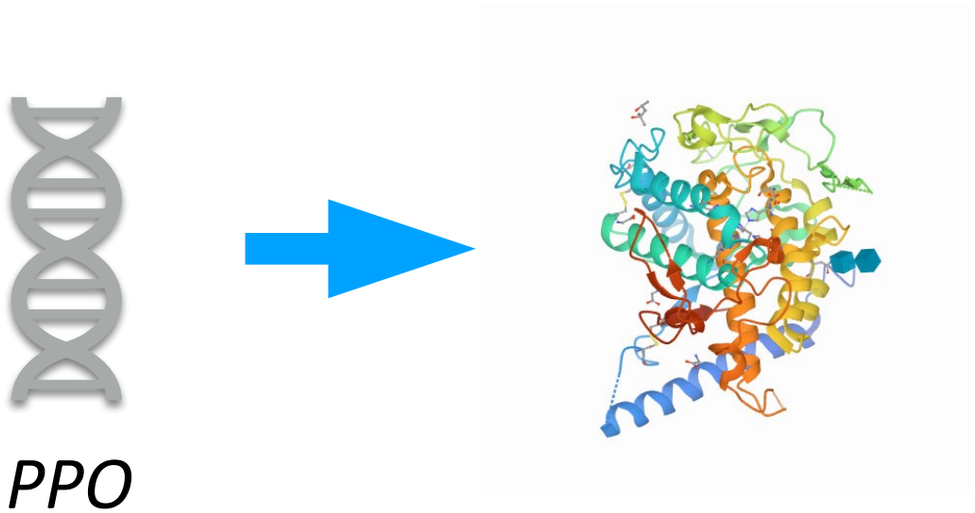
"…. the limitations of what germline editing can achieve in terms of genetic enhancement are biological rather than technological." Sarkar 2021, p. 145

In particular, pleiotropy trumps specificity of gene action.

3.2 - Crispr and human germ line editing

CCR5 has a putative causal role in lungs, liver, brain and immune system functioning. This means that it has a **pleiotropic effect**, not a specific one like (supposedly) the *PPO* gene in the mushroom case (A CRISPR definition of genetic modification. Nature Plants 4, 233 (2018). https://doi.org/10.1038/s41477-018-0158-1).





3.3 - Crispr and human germ line editing

But there is another aspect of the He Jiankui's case that is instructive.

Victor J. Dzau, president of the US National Academy of Medicine, Marcia McNutt, president of the US National Academy of Sciences, and Chunli Bai, president of the Chinese Academy of Sciences quickly wrote an editorial after He's pronouncement.

They wrote: "The Second International Summit on Human Genome Editing, held in Hong Kong last month, was rocked by the revelation from a researcher from Shenzhen that twins were born whose healthy embryonic genomes had been edited to confer resistance to HIV." Dzau et al. 2018

3.4 - Crispr and human germ line editing

They continued: “Despite widespread condemnation by the summit organizing committee, world scientific academies, and prominent scientific leaders that such research was “deeply disturbing” and “irresponsible,” and the launch of an investigation in China into the researcher's actions, it is apparent that the *ability to use CRISPR-Cas9 to edit the human genome has outpaced nascent efforts by the scientific and medical communities to confront the complex ethical and governance issues that they raise*.” Dzau et al. 2018 (italics added)

3.5 - Crispr and human germ line editing

"…. this case highlights the *urgent need to accelerate efforts to reach international agreement* upon more specific criteria and standards that have to be met before human germline editing would be deemed permissible …. *To maintain the public's trust* that someday genome editing will be able to treat or prevent disease, the research community needs to take steps now to demonstrate that this new tool can be applied with competence, integrity, and benevolence." Dzau et al. 2018 (italics added)

3.6 - Crispr and human germ line editing

“…. the Science editorial implicitly acknowledged that there were at the time no pertinent rules in place at any level to regulate gene editing. (The state of affairs is not much better today.) This situation has the implication that He was being criticized for violating nonexistent rules which hardly seems fair.” Sarkar 2021 p. 99

Again, local governance is not enough to avoid the repetition of He’s case. This is an issue pertaining to global ethics.

There seems to be a political vacuum in this sense, if not an unwillingness for global governance.

Let us pass to human enhancement.

3.7 - Crispr and human germ line editing

“Our future is in our hands now, whether we like it or not. But by not allowing enhancement and control over the genetic nature of our offspring, we consign a person to the natural lottery, and now, by having the power to do otherwise, to fail to do otherwise is to be responsible for the results of the natural lottery. We must make a choice: the natural lottery or rational choice. Where an enhancement is plausibly good for an individual, we should let that individual decide. And in the case of the next generation, we should let parents decide.” Savulescu, J. 2005. New breeds of humans: The moral obligation to enhance. Ethics, Law and Moral Philosophy of Reproductive Biomedicine 1: 36–39. pp. 38-9

3.8 - Crispr and human germ line editing

Biologically speaking, acting on the genetic basis of, for instance, cognitive traits is less safe than eradicating mono-genetic diseases: cognitive traits surely have a pluri-genetic basis and, by assumption, pleiotropy is rife.

What is the argument in favour then?

Savulescu's argument is based on the promotion of well-being. As a consequentialist and utilitarian, any action or policy should be judged on the basis of what outcomes it produces, where the ultimate good is the maximisation of well-being.

But if this is the case, why should we bother with enhancing cognitive ability or physical appearance?

3.9 - Crispr and human germ line editing

“As Sparrow has pointed out, we should directly engineer people with brains designed with appropriate neurotransmitters generating an overwhelming sense of well-being …. Alternatively, if we are so able, we could manipulate genes so as to ensure that negative feelings do not arise, for instance, by mutating putative genes associated with depression. Genetic enhancement would thus no longer be dependent on the traits that liberal eugenicists had originally promoted. Rather, genetic enhancement would take a short cut to the genes most directly promoting well-being.” Sarkar 2021 p. 124

3.10 - Crispr and human germ line editing

Furthermore, if maximising well-being is the issue, Sarkar (2021, p. 125) also argues that "…. to enhance beyond the normal functional level, there is no evidence, nor any other compelling reason to believe, that we would be increasing well-being of that individual."

The more intelligence = more happiness equation seems wrong.

Is the argument actually that a society with cleverer people is better than a society with stupider people? This would not be liberal eugenics, as it requires social planning.

The burden of proof for the legitimacy of human enhancement is on the shoulders of its advocates.

4.1 -The locus of medical intervention

Another instructive aspect of the debate concerning germ line editing pertains to the level of medical intervention.

Medical intervention could be through the manipulation of the (extra-genomic) environment or through genetic manipulation.

Even supposing that CRISPR is very refined, often the best locus of medical intervention is not the genetic.

I can intervene, for instance, by adding folic acid to flour in order to reduce the incidence of pregnancy complications in a population.

4.2 -The locus of medical intervention

Even in the case of protein-based molecular diseases caused by single genes, environmental intervention is often most appropriate.

Consider PKU (phenylketonuria). This is a genetic disease caused by homozygosity for two defective (i.e., mutated) alleles coding for the phenylalanine hydroxylase (PAH) enzyme, which normally metabolises phenylalanine.

Phenylketonuria is an ideal case for CRISPR intervention and genetic manipulation.

4.3 -The locus of medical intervention

However, even today we rely on environmental intervention in the form of diet (pretty much like Hippocrates and Galen):

“Starting in the early 1960s, first in the United States and then elsewhere, babies began to be genetically screened for PKU so that they could be immediately put on this diet if they had two copies of the allele for the disease. Sixty years later, this is still what we do today to manage PKU. Even though the prescribed diet is expensive, we have no other option.” Sarkar 2021 p. 30

4.4 -The locus of medical intervention

However, there is both a tendency to think that genes “determine” disease (or any other trait, molecular and not) and to think that there must be a biologically significant “genetic basis” for a disease (or any other trait, molecular and not):

Critics of genetic determinism and reductionism have pointed out that this way of thinking tends to downplay the causal influence of the extra-genomic environment on development, including the causal influence of the social environment.

4.5 -The locus of social policy

Concerning educational policies, many psychologists think that “educational attainment” is mainly due to genetic factors.

One chief proponent of this vision (at some point advising the UK government) is Robert Plomin.

According to a report of the UK government, Plomin’s work “…. has shown that *most of the variation in performance of children in English schools is accounted for by within school factors (not between school factors), of which the largest factor is genes*.” Sarkar 2021, p. 129 (italics added)

4.6 -The locus of social policy

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Published: 08 January 2018

The new genetics of intelligence

Robert Plomin & Sophie von Stumm

Nature Reviews Genetics **19**, 148–159 (2018) | Cite this article

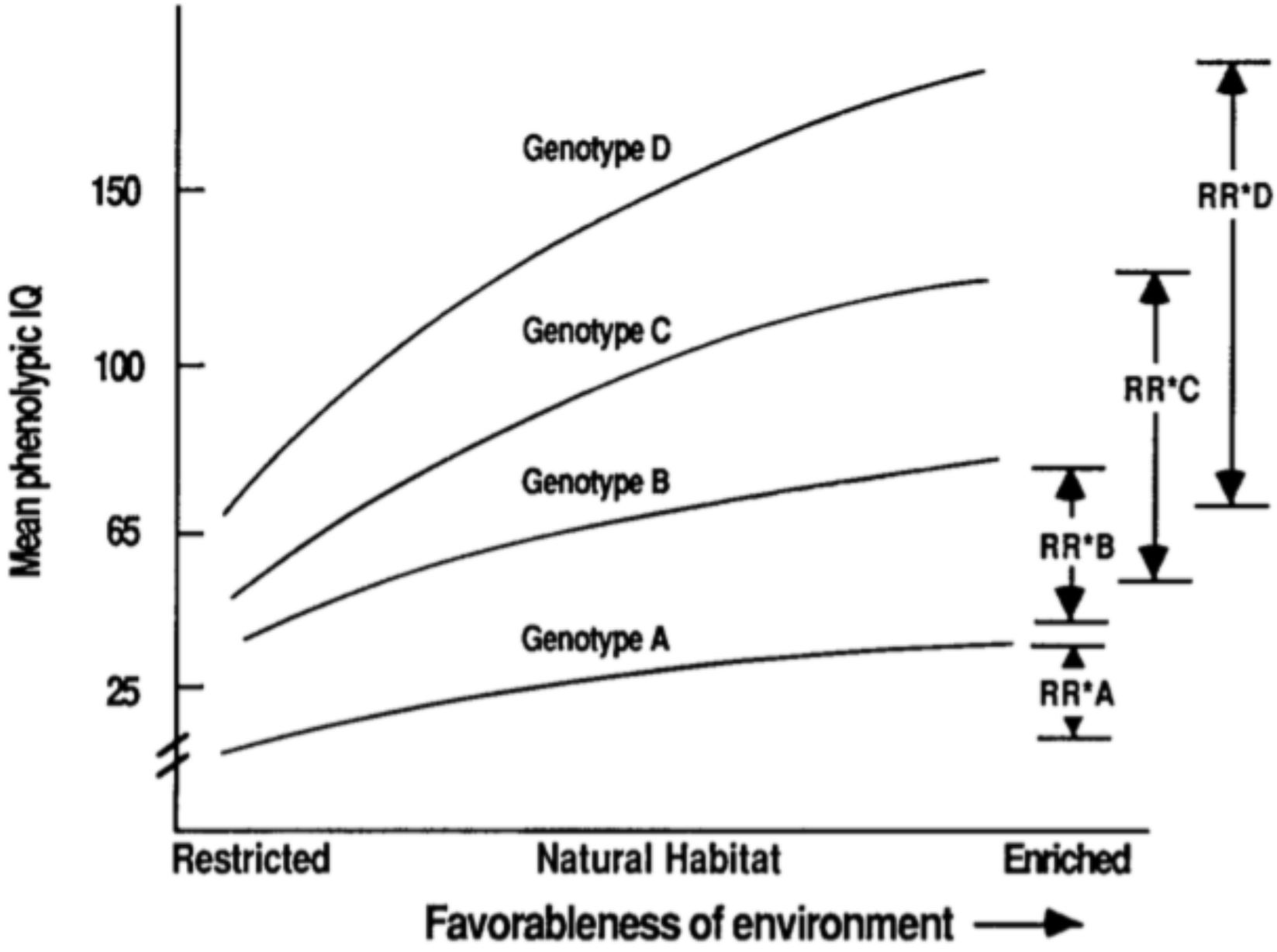
4.7 -The locus of social policy

The big idea here is that the genome poses an upper and lower limit to the developmental capacities (e.g., cognitive) of the organism.

This is the concept of reaction range first illustrated, according to Platt and Stanislow (1988), by the psychologist Gottesman, I. I. (1963).

It is, according to them, a psychological concept with no sound biological basis because: “The reaction-range concept presumes that the genotype imposes a priori limits (a range) on the expression of a phenotype.” Platt and Sanislow 1988, p. 254

4.8 -The locus of social policy



Reaction range of 4 genomes (Platt and Sanislow 1988, p. 255): can richer environments extend the reaction range?

4.9 -The locus of social policy

What are the implications of assuming a priori that the genome imposes, through the reaction range, a limit to the developmental potential of the organism?

That the manipulation of the environment cannot make a significant causal contribution to development, that it cannot extend developmental potential (e.g., educational attainment).

Hence, for the state to invest in education does not make much sense, as most of the variation in educational attainment is accounted for by genes, not social disparity (between school factors, see slide 4.5).

For many critics, this is ideology, not sound biology.

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