Unit: Reductionism in Biology and Medicine

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1. Gene editing to change a phenotypic trait presumes:

   i. The candidate gene is responsible for the emergence of the trait in the organism. (Here "responsible" can be flushed out in a variety of ways for philosophical purposes. One option would be to hold that the gene in question *causes* the trait.)

   ii. Intervention at the genetic level would be successful in changing the trait.

2. Notice that there is an asymmetry here. Genes are privileged over the phenotype. We can reacast this to say that the genotypic level is privileged over the phenotypic level.

3. A related but different way of viewing this privilege is to say that the genotypic level explains the phenotypic level.

   - We will call this *epistemic* privilege. Here "epistemic" is used to indicate that knowledge at the genotypic level is privileged.
   - Thus the genotypic level is epistemically privileged over the phenotypic level.
   - This is the thesis of genetic reductionism.

4. Genetic reductionism was the dominant ideology of twentieth-century biology.

   - We will shortly analyze why and how genetic reductionism came to be so dominant.
   - It should be obvious that genetic reductionism is what generates the expectations that drove the Human Genome Project.
   - The expectation that CRISPR-based gene editing will be a game changer for medicine (and industrial biology) is also predicated on an assumption of genetic reductionism. (If genes are not the right level to intervene to change traits, what's the point of editing genes?)

5. What drives genetic reductionism? First (and most important) part of the answer.

   - The undeniable success of genetic explanation in a spectrum of important biological situations cannot be denied.
   - While development is a result of a complex historically contingent interactions between organisms and environment, and within organisms, between DNA and its physical environment, all mediated by physical law and sometimes chance factors, DNA remains a critical molecular resource.
   - Some philosophers and psychologists such as supporters of so-called Developmental Systems "Theory" (DST) have denied this and argued for a "parity" thesis putting genes on par with non-genetic factors—all this shows is a remarkable lack of understanding of basic biology.
   - The success of genetic explanation became obvious more than a century ago, with the work of Thomas Hunt Morgan and his school at Columbia University in the 1910s. (Hermann J. Muller imported it to the University of Texas in the 1920s.)
     - Working with he fruit fly, *Drosophila melanogaster*, Morgan and his school mapped hundreds of traits to chromosome (though the fact that genes were specified by DNA rather than proteins or some other molecule was only established in the 1940s).
     - This strategy of identifying genes through segregation and, especially, linkage analysis was subsequently extended to thousands of species before being replaced by molecular techniques that superseded them in most non-human organisms after the molecular revolution in biology in the 1950s.

- Starting in 1949, with Pauling's work on sickle cell disease, physically specific mutations in genes were demonstrated to cause diseases. By now, hundreds of "monogenic" diseases and thousands of conditions are known.
- **However**:
  - When we look at the bewildering variety of structural traits that organisms have, let alone behavioral traits, the number which have a clear genetic etiology is miniscule.
  - We know most about these because these are the ones biologists focused on in the twentieth century. They had these focus because these were easier to study using the mostly genetics-based toolbox that most biologists were familiar with. There was a tremendous *selection bias* (to borrow a term from statistics).
  - Whenever we have turned to complex traits, for instance, human behavioral traits (including mental traits), claims of genetical etiology get lots of popular press but inevitably seem to disappear as more data roll in (though that part is not reported in the press). Recall the popularity of the "one adjective-one gene" hypothesis in the 1980s that helped generate public interest and support for the Human Genome Project.
  - The failure of genetic reductionism has thrust epigenetics into the limelight since 2000. There is not compelling evidence for trans-generational epigenetic inheritance (violating yet another twentieth-century dogma) even though its extent and its importance for evolution remains far from clear.
  - These matters are treated in some detail in Sarkar (1998) which remains the most comprehensive assessment of genetic reductionism but clearly needs to be superseded using what we have since learned about biology, especially through epigenetics.

6. What drives genetic reductionism? Second part of the answer.

- The reservations just mentioned suggest that genetic reductionism not only has a seriously delimited scope but, because these limitations most clearly exclude complex phenotypes, it has limited medical applicability.
- However, there has been another kind of reductionism that has been immensely successful and important for biology in the twentieth century.
- This is *physical* or molecular *reductionism.*
- The two levels are: the biological (or "living") and the physical (or molecular) *at the structural scale of macromolecules.* (The limitation to this structural scale is important because, once we go to the atomic or sub-atomic level, reductionism becomes a very doubtful proposal.)
  - The physical level has epistemic privilege.
  - Moreover, unlike the case of genetic reductionism, we have a new and very important factor: the physical level conists of components (or parts) of biological wholes.
  - Thus the whole is explained in terms of the parts. (The parts enjoy epistemic privilege.)
  - One major surprise was that the interactions between macromolecules are very weak from a physical point of view, hundreds of times weaker than the covalent or other bonds that hold the macromolecules together.
  - Structure determines function: this served as one of the most important slogans of early molecular biology (of the 1950s and 1960s). Structure refers to shape and size.
  - The central figure in developing this view of life was Pauling.
- Two models exemplify this kind of thinking at its most powerful. They were developed in the late 1950s and early 1960s by the Pasteur Institute group surrounding Monod and Jacob. These models showed how traditional exemplars from the anti-reductionists' repertoire could be successfully resolved from a reductionist perspective. For details, go to your reading (Sarkar 2002).

  (a) The *operon* model showed how goal-directed behavior could be accounted for using ordinary physical interactions. Thus, we have a "taming of teleology."

(b) The *allostery* model showed how co-operative phenomena could be accounted for using ordinary physical interactions. Thus the "whole was **no** more than the sum of its parts."

- The success of molecular biology is the success of physical (or molecular) reductionism.
- The success of physical (or molecular) reductionism finally made materialism about biology something other than speculation. No matter how plausible that speculation had been in the past, it had not been supported by hard scientific results.

7. The importance of keeping genetic and molecular reductionism distinct cannot be over-emphasized.

   - To drive the point home, recall that genetic reductionism achieved its most important successes back in the 1910s when no one knew how genes were physically specified. In fact, most ideas about the physcial or chemical nature of the gene up to the end of the 1930s turned out to be completely wrong.
   - Using the (undeniable) success of molecular biology to promote the Human Genome Project invovles an illegitimate conflation of genetic and physical (or molecular) reductionism.
   - It constitutes the use of the value of the latter to promote the former in spite of its dubious status when it comes to complex phenotypes.

References:

- Sarkar, S. 1998. Genetics and Reductionism. New York: Cambridge University Press.
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- Sarkar, S. 2002. Genes versus molecules: How to, and how not to, be a reductionist. In van Regenmortel, M. and Hull, D. L. Eds. Promises and Limits of Reductionism in Biomedical Sciences. New York: Wiley, pp. 191 –206.