CONCEPTUAL CHANGE AND SCIENTIFIC PROGRESS IN GENETICS

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This is to certify that we have read this thesis and that in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Doctor of Philosophy.

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ABSTRACT

CONCEPTUAL CHANGE AND SCIENTIFIC PROGRESS IN GENETICS

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In this thesis, the historical origins and the contemporary status of the gene centric perspective is evaluated. Gene centrism is a viewpoint which is characterized by the emphasis on genes in the explanation of phenotypes. Gene centric perspective has been defended on the grounds that only genes bear information that specifies organisms. The information concept, as it is used in biology, is problematic. Gene centrism cannot be grounded on a problematic concept of information. The real power of gene centrism depends on the success of genetic analysis as a method for investigating biological phenomena, rather than a fundamental theory based on the concept of information. Complex phenoptypes and their genetic bases, for which genetic analysis reaches its limit, provide clues for how the limits of gene centrism would be transgressed.

Keywords: Gene centrism, genetic information, genetic determinism, genetic program, scientific progress.

ÖZ

GENETİKTE KAVRAMSAL DEĞİŞİM VE BİLİMSEL İLERLEME

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Bu tezde gen merkezci perspektifin tarihsel kökenleri ve güncel durumu değerlendirilmektedir. Gen merkezcilik, fenotiplerin açıklanmasında genleri vurgulanmasıyla karakterize edilen bir yaklaşımdır. Gen merkezci perspektif, genlerin organizmayı belirleyen enformasyonu taşıması üzerine temelendirilmiştir. Biyolojide kullanıldığı biçimiyle enformasyon kavramı sorunludur. Gen merkezcilik sorunlu bir enformasyon kavramıyla temellendirilemez. Gen merkezciliğin asıl kuvveti, enformasyon kavramına dayanan temel bir kuramdan ziyade, genetik analizin tarihsel olarak, biyolojik görüngüleri irdelemek için başarılı bir yöntem sunmasından kaynaklanır. Genetik analizin yetersiz kaldığı karmaşık fenotipler ve bunların genetik temelleri, gen merkezciliğin sınırlarının nasıl aşılacağı konusunda ipuçları sunmaktadır.

Anahtar Kelimeler: Gen merkezcilik, genetik enformasyon, genetik program, bilimsel ilerleme.

To My Wife Semay,

Whose labor for this work is invisible to most, but not for me.

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INTRODUCTION

1.1 Colorful Tales About Genetic Information and the History of Genetics

Top newspapers report genes for violence, terrorism, psychiatric diseases, sexual orientation, years of schooling, obesity or whatever human trait imaginable.[1]Genetic explanation invades every field of biology and related disciplines. The idea of selfish genes programming the organisms for their own replication has occupied the imagination of many people for 40 years, till Richard Dawkins published his *The Selfish Gene.*

Genetics provides many important philosophical questions. For instance, "what is genetic causation?" is an interesting philosophical question because it is related to the ages old metaphysical issues about causation as well as ethical issues such as fatalism and moral responsibility. Is it possible to single out one type of cause among others in an interactive system? If genetic causation implies determinism, could we hold anyone responsible for her/his actions?

This thesis is not about the ethical or political dimensions of the problem of genetic determination of human behavior. It is more about how the science of genetics evolved and what made genetics such a progressive science. To uncover the conceptual underpinnings of genetic explanations, it is useful to look at the history of this science. In history, and especially in the founding periods of a science, one can see the emergence of the core concepts and the tools in their simplest form. For instance, the gene concept and its evolving meaning can be understood better if we

[1] See Knapton (2014), Rangela (2015), Stallard (2014), Devlin (2015), Sample (2016) for such reports.

investigate the scientific problems it was invoked to solve. This historical outlook provides insights into the reasons of conceptual change and progress in genetics.

Genes have come into center stage in biology in a lengthy process. Gene centrism means that genes have a privileged role in the explanation of phenotypes. Gene centrism has traditionally been defended on the grounds that genetic causation is a special kind of causation. According to this viewpoint, genes are special causal agents because they carry the information to build the organism.

In this thesis, it will be claimed that gene centrism should not be justified by the concept of biological information. Genes have gained prominence in biological explanation for their function in tracking phenotypic differences. History of genetics shows that information concept was appropriate only in a very limited domain, protein synthesis. But gene centrism demanded more, a grounding theory that would justify the special role of genes in life processes. Information concept seemed to provide such a framework, but all that was achieved by using information and related concepts was to create a mirage of a unifying theory. While abstracting away the details of crucial biological mechanisms such as protein synthesis, development or reproduction, information metaphors transformed the specific causal action of these mechanisms into a vague discourse that acts as a unifying theory.

Muller (1966) gave a comprehensive defense of the gene centric perspective, which is the ancestor of modern versions. His title suggested that genetic material is the "initiator and organizing basis of life". He compared two perspectives about the origin and essence of life in order to make the gene centric perspective more precise: the metabolism centered viewpoint of life and the gene centered viewpoint of life. Metabolism centered viewpoint focused on the self maintenance of organisms by means of coordinated biochemical relations. Those reactions happened in the cytoplasm, so, the basis of life was the cytoplasm. The gene centric perspective, on the other hand, focused on reproduction. In this perspective, metabolic activities can maintain a living form only for a single generation and for an individual organism but the continuity of life requires reproduction. And the most primitive form of

reproduction is the reproduction of the genetic material itself. Reproduction of the genetic material is more properly called replication: the making of copies. In the metabolism centered viewpoint, reproduction was deemed as an extension of metabolism. A cell assimilates, grows and this results in division - reproduction. In the gene centered perspective, the metabolic process is for the sake of reproduction. Genetic material is destined for replication, and in the passing, it guides metabolic processes and its own replication.

Gene centrism in contemporary genetics is justified on the ground that only the genetic material carries information. Information related concepts permeated biology with the advent of molecular biology. In contemporary textbooks, the action of genes in a single cell and the multicellular organism are described by information related concepts. Coding, transcription, translation, genetic program, redundancy, degeneracy, are some of the concepts that carry an explicitly informational flavor. The language of biology implies that information is an indispensable concept in biology.

Some biologists (Mayr, Williams, Crick) have defended the uniqueness of the organic world on the grounds that information is a sine qua non for life but not for inorganic beings.Information is seen as a definitive feature of living things. Crick has stated that it was possible to represent all physical processes by the transfer of energy and matter but life required the transfer of information, in addition to matter and energy. But there is no coherent theory behind these statements. Shannon's (1948) mathematical theory of communication - the only formal theory of information - is not suitable for defining unique properties of life.[2] Functions, goals and other teleological concepts are needed to define that uniqueness. There is no formal (i.e. quantitative and nomological) theory that could account for the teleological properties of organisms. Those who searched for such theories inadvertently

[2] Shannon's theory is not suitable for capturing the usage of information concepts in biology because it is not sensitive to the meaning/function of information in the proper working of an organism.

supported the theologically inspired theories such as intelligent design. Intelligent design theorists such as William Dembski (2001, 2006, 2014) are still searching for objective criteria for detecting design in nature. Design and information are sister concepts. Information and the genetic program concepts imply that the organism is like a designed object whose working is specified by an explicit set of instructions, either created by a supreme designer or natural selection. A theory based defense of the uniqueness of organisms made some biological theorists' position similar to that of creationists.

Those theorists, as philosophically minded biologists, aim for a complete, unified perspective that would explain the origin and the workings of organisms. That perspective is also expected to satisfy two other conditions: It would be consistent with the laws of physics and it would demonstrate the uniqueness of organisms. The latter would prove the irreducibility of biology into physics. But there can be no nonhistorical, *a priori* reason for the irreducibility thesis. The only reason is that organisms are the products of history. And there can be no formal theory, no a priori form of history. This is why information, design or any other objective criterion is not suitable to ground the uniqueness of organisms. Only history can ground that uniqueness and that grounding requires concrete historical-causal pathways rather than general theoretical speculations.

Information concept in biology is used in a metaphorical sense. As Maynard-Smith has observed, there is no formal isomorphism between biological processes and information transfer systems like human language. But there are qualitative similarities. One of these qualitative similarities is the potential of producing infinite diversity from a limited set of units by means of differential combination. This productivity is made possible by the digital organization of the units of meaning and their combination, both in genetics and language. The genetic material could produce such "infinite" diversity because it had a combinatorial structure, composed of the letters of nucleotides. Language has a similar combinatorial structure composed of digital units. If this is what the uniqueness of life amounts to, it would only be a

colorful comic book, simple enough to stimulate the imagination of the lay reader and the evolutionary theoretician at the same time, but too simple to be an appropriate summary of the contemporary knowledge of biology and what the history of genetics tells us.

The history of genetics shows that information concept entered genetics 50 years after the rediscovery of Mendel's laws and nearly a century after Mendel's paper which founded genetics. This means that genetics could progress for half a century without the concept of information. Mendelian genetics did not ever represent genes as information carriers. Genes in Mendelian genetics were difference makers. The experimental methods of Mendelian genetics allowed a researcher to work with observable differences and genes were devices to explain the transmission of those differences in phenotypes.

Molecular biology was founded on the assumption that function followed structure. The ultimate units of function in the cells were proteins and their functions were determined by their structures. The question was what determined the structure of proteins. The short answer was that the structure of the genetic material did. The concept of information was a shorthand for the assumption that specific structures of macromolecules were the key to specific functions. The idea that genetic material carried hereditary information, then, implied that the genetic material determined the specific structures of functional molecules - proteins.When the concept of information was first introduced by Crick, its meaning was confined to the role of DNA in protein synthesis. The function of a gene was to carry the structural information for producing a protein. Jacques Monod extended the information concept to include the coordinated biochemical activity of an organism, as the genetic program. He, along with Francois Jacob, was the one to build the bridges between the concept of genetic information as a purely static description of the basic functional units of organisms, the dynamics of cell metabolism and the development of multicellular organisms. The so called genetic program was the key in this integration.

The idea of a genetic program emerged as a quick solution to many problems related with heredity. It implies that the genetic material orchestrates what happens in an organism. It is a quick solution for it ignores the intricacies of the developmental process. As a concrete model for development or evolution, it is too simple to be true. But the concept itself is flexible enough to integrate new findings about the mechanisms of development and evolution

1.2 The Structure of the Thesis

This thesis consists of two parts. In the first part - 2nd to 4th chapters - the history of genetics between Mendel's paper where he described the laws of transmission genetics and the birth of molecular biology are told. This period begins in 1865, when Mendel published his founding paper and ends in 1961, the date when the first model of gene regulation was proposed. There is a special emphasis on the evolution of the gene concept in the first part.

In between the two parts, there is a methodology chapter which summarizes the history and connects the first two chapters to general philosophy of science issues. The second part - chapters 6 and 7 - deals with the modern debates on genetic determinism and gene centrism. A chapter by chapter summary is given below.

The second chapter deals with the question of how the concepts of gene and gene action in Mendelian genetics experienced revisions for capturing an ever growing set of inheritance phenomena. Most important conceptual revision involved the multifactorial theory and the genotype conception of heredity. These conceptions, while replacing the simple one to one relations between genes and phenotypes, also made complex patterns of inheritance tractable in the Mendelian framework. In other words, they were conservative with respect to the basic laws of genetics and revolutionary with respect to the explanation of complex phenotypes. A drawback of Mendelian genetics, and even the most sophisticated forms of it, was that it relied on phenotypic differences as indirect guides to gene structure and function. This is why Mendelian genetics is represented as only indirectly dealing with genes.

In the third chapter, the birth of molecular biology is examined. The more direct approach to genes and their functions came with the advances in biochemical genetics of microorganisms and structural chemistry of big molecules such as proteins and the DNA. The emerging viewpoint was that genes specified protein structures. In the third chapter, the birth of the informational framework was also examined and it was found that the concept of information was appropriate only in providing a model for the relation between genes and proteins. The model was coding - the letter by letter determination of amino acid sequence by the nucleotide sequence.

The fourth chapter focuses on how genes were represented in evolutionary genetics. Gene centric vision and the concept of information has been defended mostly by evolutionary biologists in order to point to the uniqueness of the living world. However, the history of evolutionary genetics shows that no information concept was used in the construction of the first population genetic models of evolution. Evolutionary genetics was no different from Mendelian genetics in its conceptualization of genes. Genes were difference makers with respect to the fitnesses of organisms. A crucial difference, however, was that the models dealt not with individual genes in a handful of generations but with the evolutionary trajectory of genes by tracking the changes in their frequencies in Mendelian populations. Representing evolution as changes in gene frequencies is a methodological simplification but later it was turned into the gene selectionism of Richard Dawkins and his intellectual ancestor George C. Williams. For Dawkins, genes were the ultimate units of selection and individual organisms were temporary vessels that carried these genes across generations. This was a concise form of the gene centric vision regarding evolution. In addition, Dawkins' vision substantially used information related metaphors such as genes programming the behavior of organisms.

In the fifth chapter, the question of progress in genetics and its relation to the grand theory is discussed. Lakatos' idea of positive heuristics explain some dimensions of progress in genetics very well. Kenneth Waters' preference for "investigative

pragmatics" over a theory centered view of the organization of genetic research explains why genetics became so central for all areas of biological research better than the information based grand theory.

The other half of the thesis consists mainly of modern debates revolving around the role of the gene concept in biological explanations. In the sixth chapter, I tried to make genetic determinism more precise by the conceptual tools of modern genetics. The upshot is that genetic determinism cannot be made precise and it should be replaced by the more research directed concept of genetic determination. To put it in another way, the interesting question about most important traits such as common diseases or dimensions of behavior is to identify the role of genes in the etiology of those phenotypes. One dimension of the problem is to devise models to interpret association data. Modern genomic studies identify many genomic regions that are associated with diseases and other complex phenotypes but the important question is to make this knowledge usable in a mechanistic explanation of phenotype formation.

The seventh chapter deals with the general problem of situating genes in the more comprehensive context of biological explanation. Gene centrism, as the name suggests, puts the emphasis mostly on genes. Another approach, Developmental Systems Theory, called for a revision in almost every aspect of the gene centric perspective. Some DST thinkers offer a very radical theoretical revision, such as abandoning the terminology of information altogether. For DST, information concept and the gene centric viewpoint offers an impoverished vision of development, akin to the older theories of preformation. The strong interactionism of DST proponents seem to be too far fetched for the practicing scientist and gene centrism still has empirical and methodological support. But this support has nothing to do with an ill defined concept of information. Genes are central in biology for two reasons. Firstly, DNA is a static data source, easy to handle, analyze and manipulate once obtained. The second reason is that DNA based inheritance is the only dedicated inheritance system in the living world. These points are adequate in defending a modest form of

gene centric vision, without proposing grand theories based on the concept of information.

CHAPTER 2

MENDELIAN GENETICS: THE EXPERIMENTAL STUDY OF INHERITANCE

2. 1 Introduction

Biology is a science that deals with *developing*, *self-maintaining*, *reproducing* and *evolving* systems. Inheritance is another biological process that crosscuts all of these four processes. A system of inheritance constrains what can be passed from parent to offspring and thus, it constrains how the offspring will develop and evolve. Without inheritance, there would be no cumulative evolution, developmental regularities would be under the control of mysterious powers, and reproduction would be *de novo* creation of progeny.

An advantage brought by this centrality of inheritance is that, by studying inheritance, one can learn a lot about those four definitive processes of organisms, and even gain control over some of them. Like in the old saying "all roads lead to Rome", all biological processes are somehow related to inheritance. But this centrality also brings with it a disadvantage: all the complexities of development, survival, reproduction and evolution are reflected onto the study of inheritance. The study of inheritance is, in a sense, contaminated by the intricacies of these processes. Old theories of inheritance such as Weismann's germ plasm and Darwin's pangenesis were theories of inheritance and development at the same time and they had been proposed in an evolutionary framework.[3] They depended on experimental and observational evidence but they didn't lead to an experimental science such as

[3] John Maynard Smith and Eörs Szathmary claim that Weismann's theory of germ-plasm did separate problems of inheritance from problems of development (2009, p. 243). This is only partly true. In Weismann's theory, the development of an organism can not influence the hereditary constitution of its germ cells but the hereditary constitution determines its course of development (Weismann 1883).

Mendelian genetics. The difference probably lied in the preference on Mendel's side for careful experimentation, quantification of data and simple interpretation over grand theories encompassing development, inheritance and evolution at once.

In experimental fields of biology, progress comes not through all encompassing theories but by making biological problems amenable to experimental grasp. Biologists talk more about research strategies and frameworks than theories. They prefer to talk about "attacking" a problem rather than offering complete solutions. "Working hypotheses" are preferred over neat, theory based definitions. Here are two representative quotes from experimental biologists:

"A framework is not a detailed hypothesis or a set of hypotheses; rather, it is a suggested point of view for an attack on a scientific problem, often suggesting testable hypotheses." (Crick and Koch 2003)

"While this interpretation is at present rather highly speculative, it is just such treatments that state fundamental biological problems in ways in which they can be attacked profitably at a chemical level." (Beadle 1945a, p. 77)

These points are not raised in order to lessen the value of theorizing in biology. Rather, they show where theory gains its value in the context of experimental biology. Theory, however incomplete, speculative and simplified it seems, is valuable as much as it guides research. Mendel surpassed his contemporaries not because he had a more complete or better grounded theory, but because he made the phenomena of inheritance experimentally workable by describing an attack route.

2.2 Mendel: The Birth of Genetic Analysis

Mendel is considered by many as the founder of genetics.However, Mendel was not the first person who dealt with the problems of inheritance, neither practically nor theoretically. By animal or plant breeding, our ancestors must have gained immense knowledge about how to make hybrids, how to improve stock or how to create new plant varieties. The first theory of inheritance was Hippocrates' and it is very similar

to Darwin's theory of pangenesis (Sturtevant 2001[1965], p. 1). In short, we had practical knowledge on how to handle inheritance phenomena and theories to account for them, for thousands of years. Before the rediscovery of Mendel's 1865 paper, there were many theories of inheritance such as Weismann's theory of germ-plasm, Darwin's pangenesis, Hugo de Vries' intracellular pangenesis, Galton's Law of Ancestral Inheritance, etc. So, Mendel's theory was not the only contender. Then, the question becomes what makes Mendel's discovery so special. The question might be reformulated as such: Why do we consider Gregor Mendel as the founder of genetics? The reason, I believe, lies in the systematicity of his experiments and the clarity of his interpretation of results. These merits are apparent from his groundbreaking paper.

Mendel's paper begins with an assessment of previous hybridization research in plants. According to Mendel, earlier studies have established the constancy of some characters in hybridization beyond doubt. In other words, it was already known before Mendel that reappearance of some characters in repeated hybridization between the members of same species followed a regular pattern. But no general law of this regularity had so far been discovered. For Mendel, discovering such laws required systematic and extensive experimentation and this was lacking in previous research:

> Those who survey the work done in this department will arrive at the conviction that among all the numerous experiments made, not one has been carried out to such an extent and in such a way as to make it possible to determine the number of different forms under which the offspring of hybrids appear, or to arrange these forms with certainty according to their generations, or to ascertain their statistical relations. (Mendel 1865 in Bateson 2009, p. 41)

In this oft cited passage, Mendel gives three reasons explaining the inadequacy of earlier studies. The first reason is that early studies could not categorize the offspring of hybridization experiments into distinct categories and could not determine the numbers of offspring that belonged to each category. The second reason is that early studies did not keep track of the parent-offspring relations in a precise manner. Perhaps, fertilization process was not truly under the control of the experimenter, resulting in an uncertainty about ancestry, or the experimenters didn't continue

hybridization for multiple generations. The result of these faulty procedures is that invariant and general statistical relations between types of offspring or between offspring and parents could not be discovered - which is the third reason Mendel offers for why early studies were inadequate.

The superiority of Mendel's work can't be explained by these methodological points alone. The choice of experimental organism and the characters examined made a critical difference. Mendel chose *Pisum sativum* because:

1. It contained constant differentiating characters.
2. It was possible to prevent fertilization by foreign pollens.
3. Hybridization should not significantly affect fertility. (Ibid. p. 42).

Constancy of characters, in Mendel's terminology, means that self-fertilization of a plant produces offspring that are similar to the parent with respect to the character examined. Self-fertilization, or selfing, produces pure lines, or varieties. When the pollen from one such pure line fertilizes the seed of another, identical type, the offspring should be identical to the parents.

A differentiating character is a character which has "easily and certainly recognizable" distinct forms (Ibid). In *Pisum sativum*, there are constant differentiating characters such as yellow/green, round/wrinkled, tall/dwarf, etc. These constant character pairs make it easier to keep track of character transmission.[4] *Pisum sativum* provided an advantage over other possible experimental organisms because there were already established varieties with constant differentiating characters.

In hybridization experiments, the experimenter should have absolute control over who fertilizes who. Foreign pollens would devastate a hybridization experiment because in such a case, the pollen might have an entirely different hereditary constitution from what is intended. *Pisum sativum* provided an advantage in this

[4] Mendel (1865) makes no explicit distinction between the transmission of a visible character and it's hereditary basis except his discussion about the hereditary constitution of germ cells.

regard too. Its sexual organs (i.e. anthers and stigma) are in a capsule and this protects it from fertilization by foreign pollens. When the time for fertilization comes - when the flower opens - its own pollens already have covered the stigma (Ibid.p. 43). Artificial fertilization is achieved by cutting this capsule (i.e. keel) before the flower opens and pouring the foreign pollens, before self-fertilization occurs. Mendel observed 10.000 individual plants in his experiment and only a few of them were fertilized by false pollens (Ibid. p. 48).

Hybrid fertility is another factor that could affect the numerical relations expected in a hybridization experiment. If the fertility is reduced for some hybrids and completely lost for others, the experimenter can't observe every possible combination of characters and can't see the exact numerical relations among them. Mendel's analysis is aimed at finding the actual frequencies of characters in offspring and constructing laws out of these frequencies. These laws should go beyond actual frequencies, they should show what is possible under a wide set of conditions and for every trait. Reduced fertility would complicate matters because it would distort the frequencies in an irregular fashion. Mendel assures us of the fertility of all *Pisum* hybrids he studied.

Mendel's experiments lasted for 9 years. In the first two years, he selected 22 pea varieties with seven differentiating characters and observed whether these characters were constant. It was certain at this point that the choice of the experimental plant and the characters was good enough. Then, in the next 7 years, he proceeded with the experiment.

Mendel's experimental method consisted of 4 steps. In the first step, pure lines with alternative characters were crossed and hybrids were created. For instance, a plant with yellow seeds was artificially fertilized by the pollen of a plant with green seeds. He made reciprocal crosses so as to ensure that whether the character came from the female or from the male (i.e. pollen) made no difference. First generation consisted entirely of hybrids. These hybrids were more similar - if not identical - to one of their parents. In other words, only one of the characters showed up in the hybrids. This

was the dominant and the other was the recessive. Mendel defined dominance and recessivity as such:

> Henceforth in this paper those characters which are transmitted entire, or almost unchanged in hybridization, and therefore in themselves constitute the characters of the hybrid, are termed the *dominant*, and those which become latent in the process the *recessive*. (Ibid. p. 49).

Clear-cut dominance and recessivity relations among alternative characters made the classification of progeny easier. Mendel emphasized that the disappearance of the recessive character was not permanent. Recessives reappeared in the next generation. None of the hybrids had intermediate characters.

The second step was to self-fertilize the hybrids. The results of self-fertilization were remarkable. Both the dominant and recessive characters reappeared with a ratio of 3:1. For instance, the ratio of round seeds to wrinkled seeds was 5474:1850=2.96:1, which was very close to 3:1. For yellow/green pair, the observed ratio was 3.01:1. All seven character pairs had approximately the same ratio. The lawful relation seemed to be emerging out of these experiments.

At this point, Mendel came up with an important assumption. He said that dominants - 3:4 of the total seeds - could be further divided into two subgroups. He expressed this idea with the following remarks:

> The dominant character can have here a *double signification* -vis. that of a parental-character, or a hybrid-character…. As a parental character it must pass over unchanged to the whole of the offspring; as a hybrid character, on the other hand, it must observe the same behavior as in the first generation (Ibid. p. 55).

"Dominant as a parental character" describes the situation in which self-fertilization produces only the dominant character. In modern terminology, it refers to homozygote dominant. "Dominant as a hybrid character" refers to the character of hybrids, when self-fertilized, produce both the dominant and the recessive character. In modern terminology, it is called the heterozygote dominant.

In order to determine whether a plant is parental-dominant or hybrid-dominant, it should be further self-fertilized.[5] For every character pair, Mendel found out that 1:3 of all dominants produced only dominant character plants and 2:3 produced exactly the same ratio obtained by the self-fertilization of the hybrids (i.e. 3:1 dominant/recessive). So, the real distribution was

1 (parental dominant):2(hybrid dominant):1(recessive).

Mendel explained this ratio by a combinatorial model. In this model, the first hybrid carried both the dominant and the recessive character. Let the dominant character be *A* and the recessive be *a*. Then, the hybrid plant could be represented by *Aa*. If this plant is self-fertilized, that is *Aa* is crossed with *Aa*, the resultant distribution of progeny will be: AA:2Aa:aa. However, for this ratio to be realized, a further assumption must be made with respect to gamete formation and fertilization. A hybrid (Aa) should produce each type of gamete (*A* and *a*) with equal frequencies and each combination event should be equiprobable.[6] These assumptions were essential to the validity of Mendelism and Mendel had to give an experimental proof of them. This consisted of the last step in his experiments, but before that, he analyzed the case of multiple hybrids in order to show that the regular pattern can be extended to the combination of multiple characters.

The third step in Mendel's research was to produce multiple hybrids. The earlier experiments only dealt with hybridization between different forms of the same character: yellow vs. green *seed color*, round vs. wrinkled *seed form*, tall vs. dwarf *stem length*, etc. Multiple hybrids are produced by combining these characters in one plant. For instance, when a hybrid round/yellow (AaBb) seeded plant is crossed with a hybrid round/yellow (AaBb) seeded plant, the offspring would be like the following, given that round and yellow are dominant: Yellow-Round, Green-Round,

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[5] This procedure is not needed for recessives because they immediately establish pure lines.

[6] One might think that *Aa* is more probable because it's frequency is two times higher than the other two combinations. But in fact, it consists of two combination events: *A* with *a* and *a* with *A*.

Yellow-Wrinkled and Green-Wrinkled. Mendel found that the ratio of these offspring was 9:3:3:1. Just as the 3:1 ratio was further partitioned into 1:2:1 ratio, this distribution can further be divided such that:

4(AaBb):2(AABb):2(AaBB):2(aaBb):2(Aabb):1(AAbb):1(aaBB):1(aabb):1(AABB)

Mendel extended his analysis to three character pairs and found out that offspring frequencies obeyed the same rule: binomial distribution. The number of character pairs combined determined the number of types and frequencies of each type. For such a rule to be valid, one should assume that the distribution of one pair of characters is independent of the distribution of another pair: ".... it is demonstrated that the relation of each pair of differentiating characters in hybrid union is independent of the other differences in the two original parental stocks" (Ibid. p. 64). This is Mendel's second law which says that character pairs are assorted independently.

More importantly, Mendel suggested that this combinatorial analysis can be extended to any number of characters, and even to those characters "which appear less sharply defined in plants" (Ibid.).[7]

I previously said that Mendel had to make two assumptions in order to explain the lawful distribution of characters in the progeny, i.e. 3:1 law. The fourth step in Mendel's inquiry consists of providing experimental evidence for these two further hypotheses:

> Since the various constant forms are produced in *one* plant, or even *one* flower of a plant, the conclusion appears logical that in the ovaries of hybrids there are formed as many sorts of egg cells, and in the anthers as many sorts of pollen cells, as there are possible constant combination forms, and that these egg and pollen cells agree in their internal composition with those of the separate forms.

[7] As we will see later, the extension of combinatorial analysis into "less sharply defined" traits, such as continuously varying traits, traits with no pure lines, etc. constituted the main direction of progress in Mendelian genetics.

> In point of fact it is possible to demonstrate theoretically that this hypothesis fully suffice to account for the development of the hybrids in the separate generations, if we might add at the same time that the various kinds of egg and pollen cells on the average in equal numbers. (Ibid. p. 67).

These two paragraphs state that gametes (i.e. pollens and eggs) of a hybrid plant have every possible combination of distinct differentiating characters in equal numbers. For instance, if the hereditary constitution of a hybrid is *AaBb*, all of these four gamete types will be produced in equal numbers: *AB, Ab, aB, ab*. The gametes produced from pure lines such as AABB or aabb will be AB and ab respectively.

What is said here concerns the hereditary constitution of gametes and there is no direct way to ascertain this. The hereditary constitution of developed plants is observable from their visible properties and inferable from the visible properties (e.g. yellow, round, etc.) of their offspring in hybridization experiments. But neither eggs (i.e. unfertilized seeds) nor pollens give away their hereditary constitution directly. Thus, Mendel had to rely on genetic analysis again.

At first, Mendel produced a dihybrid by fertilizing constant round/yellow (AABB) plant with the pollen of a constant wrinkled/green (aabb) plant. The hybrid was AaBb and it was expected to produce all four types of eggs and pollens with equal frequencies. To test whether this happened, Mendel prepared a test cross such that:

1) Eggs of the hybrids with the pollen from AABB.
2) Eggs of the hybrids with the pollen from aabb.
3) Pollens of AABB with the eggs of the hybrid.
4) Pollens of aabb with the eggs of the hybrid. (Ibid. p. 68).

First and third crosses are expected to give all round/yellow seeds. Second and fourth crosses are the most important because this is the first reported case of backcrossing.[8] Backcross is one of the most important analytic tools in Mendelian genetics. The

[8] It is unclear why Mendel did the first and third crosses at all. Since either the seed or the pollen is dominant for both characters (AB), the offspring will exclusively be round/yellow. So, this cross won't reveal the kinds of pollens and seeds produced. But Mendel selfed the resultant hybrids for another generation - as he did in the third step - and confirmed his expectations.

plant aabb can produce only ab pollens and seeds. Since it is recessive for both of the characters, when it is crossed with the hybrid, the offspring phenotype would clearly show the genetic composition of the hybrid. By this test cross, Mendel showed that the hybrid produced seeds and pollens ab, AB, Ab, and aB with equal frequencies.

The picture that emerged from Mendel's experiments, according to the sequence of his experiments, can be summarized like this:

1) When two pure lines with differentiating characters are hybridized, the offspring is more similar, or even identical to one of those lines. This character which shows up intact in the first generation is dominant. The other, masked character is the recessive.
2) When hybrids are selfed, the recessives reappear in the next generation. Thus, the recessive is not lost or mixed with the dominant. Differentiating characters don't blend, they are discrete.
3) Character transmission in hybrid-hybrid crosses shows a lawful regularity. The "3:1" law is the basic law from which more complex distributions in multiple hybrids can be derived. In other words, the laws are applicable to any number of pairs - although this might be practically difficult - if there is independent transmission.
4) Characters are transmitted independently of each other. That is why, crosses between multiple hybrids produce a distribution in which the "3:1" law is still valid for each character pair.
5) Hybrids produce all possible kinds of egg and pollen cells in equal frequencies and the chances of fertilization does not depend what characters they bear.

These are the generalities that emerge out of Mendel's study, in the order as they appear in his paper. Some conclusive remarks are in order.

Firstly, Mendel never deals with what is being transmitted in reproduction. He has no concept of a gene or any other term that corresponds to it (e.g. factor). He makes no distinction between the genetic makeup and observable properties, neither does he mention any *unit of inheritance*. Some genetics textbooks (e.g. Griffiths et al 2000)

ignore this and propagate the false idea that Mendel hypothesized the existence of genes:

> Mendel's explanation is a classic example of a creative model or hypothesis derived from observation and suitable for testing by further experimentation. He deduced the following explanation:
>
> 1. *The existence of genes.* There are hereditary determinants of a particulate nature. We now call these determinants *genes*….

All Mendel dealt with was heritable character pairs and their regular transmission, not the mechanisms of inheritance or how traits develop. The hereditary constitution of gametes and the reappearance of recessives are the only clues to whether Mendel had a distinction between what is inherited and what is observed. And for both of these points, all Mendel says is that characters are distinct, recessive and dominant characters are inherited intact (i.e. pure) from the pea plant to the gametes and they are recombined in fertilization according to his simple probabilistic model. Mendel did not explicitly refer to any unit of inheritance beyond the characters themselves. He talked *as if* characters themselves were the units of inheritance.[9]

Another important question about Mendel's discovery was whether those simple laws could be extended to different species and different characters. When Mendel sent his paper to Karl von Naegeli - a famous German plant physiologist - in 1866, Naegeli's reply was mostly negative (Schwartz 2008, p. 97). He suggested Mendel to try out the same experiments with another species, *Hieracium*. When Mendel did this, he saw that the results were exactly the opposite of his earlier experiments. In *Pisum*, a cross between two pure lines produced identical hybrids. When these hybrids were self-fertilized, all parental types were restored in the progeny. In *Hieracium*, the hybrids were varied whereas self-fertilization gave progeny that

[9] The distinction between observable characters and units of inheritance was introduced into genetics by Johannsen in 1909. He invented the term phenotype to refer to those properties and genotype to refer to the total hereditary constitution.

were identical to the mother plant (Ibid. p. 99). If Mendel had begun his studies with this plant, he wouldn't arrive at his neat mathematical model.[10] So, the choice of experimental organism made a critical difference in the process of discovery.

Returning to our original question, we can say that Mendel stood out among his contemporaries because his method of experimentation, his recording and interpretation of the results was like a detailed user's manual. All analytical tools of genetics was ready in a single paper. And the interpretation of results made no reference to the complexities of the mechanisms of development and inheritance. Mendel changed the focus of inheritance research from the overall similarity between parents and offspring to the transmission of individual characters. He tracked individual characters rather than whole organisms.[11] He saw characters as independent entities whose inheritance patterns should be mathematically analyzed. This makes Mendel's method applicable to a wide range of hereditary phenomena. These are the essential reasons why Mendel's discovery is not a theory among other theories. It is the beginning of a science.

However, the extension of Mendelian analysis to other species and other kinds of characters required revision and reinterpretation, as the *Hieracium* case shows. These revisions and reinterpretations concerned (1) unit characters, (2) independent segregation, (3) the mechanism of inheritance, (4) the distinction between observed characters and hereditary constitution, (5) gametic purity, (6) characters which vary continuously and (7) the nature of the units of inheritance.

[10] In fact, *Hieracium* reproduced by apomixis - a kind of asexual reproduction from the eggs alone - which was the cause of this complication. So, the hybrids were not real hybrids.

[11] Raphael Falk (2009) names this "itemization of characters".

Mendel's laws were rediscovered around 1900 by Hugo De Vries, Carl Correns and E. von Tschermak (Schwartz 2008).[12] William Bateson was one of the first scientists who immediately understood the importance of Mendel's paper. He translated the paper into English in 1901. Bateson interpreted Mendel's paper in a preformationist fashion. He thought Mendel's discovery supported the view that organisms are mosaics of individual characters which are inherited as units. This interpretation is termed the unit character theory. Unit character theory was refuted very early in Mendelian genetic research but it is still a very instructive fault because by refuting this theory, Mendelians refined their understanding about the relations between units of inheritance and observed characters.

2.3 Bateson and Unit Characters

William Bateson is the eponym of the science of "genetics". Many terms that are still used in genetics such as *allele, heterozygote, homozygote, epistasis, F1-2-3... generations* were coined by Bateson (Carlson 1966).[13] Although he is not counted among the codiscoverers of Mendel's laws, he was the most devoted and most prolific follower of Mendelism. Since he is the one who presented Mendel to the English-speaking scientific circles, his ideas were taken to be definitive of Mendelism.

In 1902, he wrote a book in which the English translation of Mendel's paper as well as the explication of his ideas and a defense of Mendelism against biometricians such as Weldon appears. In this book, Bateson deduced seven principles from Mendel's work. We will deal with only the first four of them.

[12] The details of the rediscovery will not be examined here.

[13] Bateson (1902) named differentiating characters *allelomorphs* and this term was later simplified to *alleles*.

The first principle is the principle of gametic purity. Gametic purity means that every gamete can have only one of the differentiating characters. For instance, a hybrid yellow seeded plant (i.e. *Aa*) can produce gametes carrying only one of those characters: either *A* or *a*. A gamete can neither be a hybrid nor a blend of alternate characters.

The second principle states that zygotes are classified as either heterozygotes or homozygotes. If both gametes carry the same pure character, the zygote will be a homozygote. If they carry alternative characters, the zygote will be heterozygote. According to the third principle, heterozygotes are further divided into two types. If there is complete dominance, the heterozygote will show only the dominant character. If dominance is not complete, the heterozygote will be intermediate between two pure characters.

These three principles form the core of Bateson's interpretation of Mendel. According to this interpretation, gamete formation is represented as the dissolution of a character pair into its components and fertilization as the reunion of this pair. Such a representation led Bateson to think of characters as inherited units. So, he defined *unit character* as a character that "is capable of being dissociated or replaced by its contrary" (Bateson 2009 [1902], p. 27). Previously (1901), he had written an introduction to the first translation of Mendel's paper where he defined unit characters as such:

> In so far as Mendel's law applies, therefore, the conclusion is forced upon us that a living organism is a complex of characters, of which some, at least, are dissociable and are capable of being replaced by others. We thus reach the conception of *unit-characters*, which may be rearranged in the formation of the reproductive cells. (Bateson 1901, p. 1).

For Bateson, the applicability of Mendel's law of segregation simply meant that hybridization experiments are able to dissociate and recombine character pairs. Even as of 1901, he believed that a lot of such positive results had accumulated.

Bateson was a true experimentalist, and he believed that the prospects for the extension of Mendel's laws into new domains - i.e. new species and new characters - depended on the success of such hybridization experiments.

One obstacle was that there were characters which seem to Mendelize (i.e. conform to Mendel's laws) in some hybridizations but not in others. Bateson called these characters *compound* in the sense that they are composed of multiple unit characters. To explain why they behave like single units in some hybridizations and not in others, Bateson developed an analytic scheme in which an individual can be heterozygous for many alleles that affect the same character. For instance, instead of representing a character with a single letter like *A*, Bateson represented the compound character with a combination such as A1A2A3… These new symbols shared the letter because they all referred to a single character, but they had different numerals probably because they referred to different *parts* or different *aspects* of a character. Suppose that we cross *A1A2A3B1B2B3* with *a1a2a3b1b2b3* and carried out further experiments as Mendel did.[14] In this scenario, the compound characters will act as units. But if our cross included organisms heterozygous for one or more of those numbered units, the character would dissociate further into those hidden types.

These four linked ideas - gametic purity, heterozygote/homozygote distinction, unit characters and compound characters - constitute a coherent structure but this doesn't mean that they are empirically true. Bateson had thought that apparently non-Mendelian characters could be decomposed into unit characters.[15] By this way,

[14] Here, both organisms are homozygous and thus, the symbol is a shortened version of A1A1/A2A2/A3A3/….

[15] Here, Mendelian character means a character which has distinct forms segregating in gamete formation. A non-Mendelian character is best exemplified by continuously varying characters like stature.

gametic purity would be preserved. However, the existence of non-Mendelian heritable characters can also be taken as evidence for the inadequacy of this model.

Gametic purity was the first principle that came under attack. To save it, Mendelians had to replace the unit character hypothesis with the unit factor hypothesis. This replacement necessitated Mendelians to make a distinction between units of inheritance and observable characters. Then, they had to show non-Mendelian characters - continuous characters or characters that don't segregate in a predictable fashion - had a complex genetic basis.

The attack on gametic purity came from two Harvard geneticists - William Castle and John C. Phillips - who extended Mendelian analysis to mammals. They studied coat color variation in rats and guinea pigs. The results of their studies challenged the idea that gametes were pure with respect to unit characters they transmit. The explanation of those anomalies required two things: the genotype/phenotype distinction and multiple factor hypothesis.

2.4 Johannsen and The Genotype Conception of Heredity

Unit character interpretation of Mendelian analysis postulated that there are discrete units of inheritance which corresponded to a character, segregated independently in gamete formation, and recombined - without blending - in zygote formation. Mendel's analysis didn't make it clear whether the characters themselves or some deeper structure is transmitted in inheritance. This led to some confusion: Are there unit factors in the gametes that correspond to discrete biological traits? Can those factors change in the course of transmission or development? How do they determine the final outcome of development? Wilhelm Johannsen developed a conceptual framework that would both preserve the basic

principles of Mendelian analysis and avoid those confusions.[16] The framework is called the genotype conception of heredity.

Johannsen, like Mendel, was in search for mathematical generalities in inheritance (Falk 2009). But unlike Mendel, he didn't study distinct character pairs. His studies concerned continuously varying characters such as bean size. He showed that in pure lines, size variation was absolutely due to environmental variation. He had obtained pure lines by multiple rounds of self-fertilization. The offspring still varied but variation was not heritable. The mean sizes of different pure lines, however, was heritable. The stable type was explained solely by the underlying, deeper type, the so called genotype.

Before the genotype conception of heredity was established, it was believed that the "personal qualities" (observable biological traits) of individuals were being transmitted to the offspring.[17] Johannsen calls the confused viewpoint "the transmission conception of heredity". The essential idea of this conception is that in heredity, observable properties of individuals (i.e. phenotypic properties) are transmitted. This implies that the phenotypic properties (e.g. flower color, body length) of parents cause the phenotypic properties of offspring. But according to Johannsen, heredity is a case of common causation:

> The personal qualities of an individual organism do not at all cause the qualities of its offspring; but the qualities of both ancestor and descendant are in quite the same manner determined by the nature of the 'sexual substances' – i.e., the gametes – from which they have developed. (p. 130)

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[16] Johannsen never became a Mendelian. He thought that the distinct characters Mendelians studied were superficial: they weren't important with respect to evolution or survival. He was interested in species typical hereditary properties rather than aberrations studied by Mendelians. He was a holist with respect to inheritance. Despite all his reservations about Mendelism, we might still say that he made a great contribution to Mendelian genetics by separating observable characters from their genetic basis.

[17] See Spencer (1864) and Nageli (1914 [1898]) for examples of the transmission conception of heredity.

Johannsen also distinguished the genotype conception of heredity from preformationism. According to unit-character style preformationism, there is a one-to-one correspondence relation and a one-to-one causal chain between hereditary elements and phenotypically discrete traits. Genotype conception preserves the discreteness of the elements, but proposes many-to-many relations between the elements and resulting phenotypes.

Those discrete hereditary elements (i.e. unit factors of Mendelian genetic analysis) are named as genes in Johannsen's new vocabulary. Genotype is "the sum total of all the genes in a gamete or in a zygote". Johannsen provides no structural idea concerning the nature of genes. The only properties important in Mendelian and pure-line research are that gene differences account for some phenotypic differences, genes separate in certain ratios in hybridization and genotypes are constant, at least in pure-line research.

Borrowing an idea from Woltereck, Johannsen describes genes as potentialities, which are actualized according to the environment and other genes in the genotype. Genotype, as the sum total of genes, is the totality of these potentialities. It is a norm of reaction, determining the boundaries of developmental variability. Phenotype is the actualization of those potentialities under certain environmental conditions. No linear relation between genes and phenotypes are assumed in this conception.

Genotypes were the determinants of hereditary and thus constant characters of organisms. Genotypes did not change by selection once a pure line is established. If we translate this into a Mendelian framework, we can say that genes (i.e. factors) are constant in pure lines. However, it must be kept in mind that Johannsen's studies did not concern Mendelian character pairs, easily dissociable characters that segregated independently. In a sense, Johannsen established the constancy of total genotypes in multiple generations of self-fertilization. Apart from that, his framework does not say much about the individual units of inheritance - factors or

genes - and their constancy in hybridizations. That point, the constancy of individual factors, had to be proved by Mendelian research.

One of the benefits of genotype conception was to allow for complex gene-gene interactions in the production of phenotypes. Here, interaction between genes is a functional relation. Genes come together in the formation of some character. But there is another, structural, relation between genes which first showed itself as a deviation from the Mendelian principle of independent assortment. It appeared as a deviation and then turned into an analytical tool by Drosophila geneticists in the U.S.

2.5 Linkage Mapping and T. H. Morgan's Fly Lab

What has been said so far assumes that Mendelian ratios are empirically secure. The law of independent assortment states that different character pairs dissociate independently in gamete formation. The expected ratios of offspring depend on this assumption. But exceptions to this law began gathering in early 1900s. It was shown that some characters were transmitted together. This phenomenon is called linkage, and it soon became one of the definitive tools of Mendelian research. The phenomenon was most thoroughly studied in Thomas Hunt Morgan's lab in the United States.

T. H. Morgan was at first an opponent of Mendelism because he thought if one accepts unit-character interpretation of Mendel's factors; it would lead to the dubious idea of preformationism. Preformationism was an idea that dated back to the 17th century. In short, preformationism in the Mendelian framework implied that all that is needed to make an adult organism resided in the germ cells and individual inherited factors had a direct correspondence to parts of the adult form. Mendel's studies were presented to the English speaking world by William Bateson, who had interpreted Mendel's discovery in such a preformationist fashion. Morgan at first thought that Mendel's theory in the same class as those speculative and preformationist theories

of Weismann and Herbert Spencer. Morgan's experience with embryology, his distaste for speculative theories of development, his observations on the effects of environmental factors in sex determination and his knowledge on the complexity of development made it impossible for him to accept preformationism. He was even doubtful about the chromosomes' role in heredity till one of his students; Calvin Bridges showed that sex was determined by the X chromosome, in his experiment on chromosome non-disjunction.

But how then Morgan, a Mendel-skeptic, came to be the leader of Mendelian genetic analysis in Drosophila and the construction of first genetic maps? In fact, Morgan began his Drosophila work, in 1905, to study experimental evolution, not transmission (i.e. Mendelian) genetics (Kohler 1994). He believed in De Vries' idea that organisms enter mutating periods which will end up in the creation of new species. He wanted to construct pure lines with artificial selection and was hoping to test De Vries ideas, especially whether he could observe the mutating periods in *Drosophila*.[18] He believed that the effects of mutations were smaller than De Vries type species-creating changes but were bigger than Darwinian type continuous variation.

In 1910, he first observed the "with" mutant and then the "superwith" mutant, which were pigmentation disorders. But the most dramatic change in his thinking occurred when he isolated the "white" mutant. White was a sex linked mutation that clearly showed Mendelian inheritance. It was not induced by selection, it had low frequency but became visible because the size of his experimental Drosophila population was large enough (Ibid. p.45). Kohler (1994) suggests that studies in experimental evolution necessitated big stocks and this made low frequency mutations visible. But this also led Morgan to abandoning experimental evolution and specifically focusing on transmission genetics. In experimental evolution, non-Mendelian (i.e. characters that don't segregate independently and assort randomly) characters were considered

[18] De Vries' mutation theory is covered in the third chapter.

better suited to the task. Mutations like "white" on the other hand, were abominations that weren't suitable to simulate real-world evolution.[19]

In the fly room, mutation after mutation arose. This led to a need for conceptual change, driven by the needs of experimentation (Ibid., p. 54). In classical Mendelian formulas (i.e. organ system formulas), absence and presence of certain factors were used to describe the transmission of a certain morphological character (e.g. eye color). For instance, CRPO is the classical formula for the wild type (red) eye color. C denoted the "color determiner" and when it was combined with the factors R (red), P (pink), O(orange) the resultant fly would have red eyes. When R is absent, as in C-PO, the fly would be pink eyed. When C is absent, regardless of the presence of other factors, the fly would be white eyed. Since the number of allelomorphs increased with the discovery of new eye color mutants (e.g. eosin), Mendelian formulas ceased to be useful in classifying mutations (Ibid., p. 59). In 1912, two new mutant eye colors, purple and maroon, made the formulas for eye color unmanageable (Ibid. p. 60).[20]

Another problem with Mendelian formulas and the presence-absence scheme - which was the theoretical basis of those formulas - was that they couldn't explain backward mutations in which the wild type phenotype reappears in a mutant population.[21] For instance, Morgan, in 1913, observed that a winged male in a population of pure wingless flies.[22] These types of backward mutants necessitated a different

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[19] The "mutation theory" of Hugo De Vries and the relation of Mendelism with the theory of evolution are covered in the third chapter.

[20] Indeed, any kind of linear formula of this kind is manageable. The point here is that revising established formulas every time a new mutant appears will put the trustworthiness of the Mendelian research program under doubt.

[21] Backward mutations are also called reversions or atavisms.

[22] In 1913, Morgan observed a fly with a single wing. When he crossed this fly with wingless females, he obtained only wingless offspring. Upon this, he speculated that genes are "labile aggregates" which can be rearranged in somatic cells. This kind of sloppy thinking, combined with Morgan's expressed discontent with speculations on the nature of genes might be the source of Muller's criticism of Morgan's confused ideas (Schwartz 2008, p. 196).

explanation than absence because otherwise, one must suppose that a very complex character is recreated by a single mutation. So a new model of representation was needed. This model was a linear map, which is organized spatially rather than functionally. To create such maps, Morgan and his students should discover the phenomenon of linkage.

Morgan had already found in 1911 that there are gene exchanges between homologous chromosomes and the rate of exchange was inversely proportional to the distance of genes on a chromosome. Genes that were transmitted together (linked genes) were assumed to lie near on the same chromosome while genes that were transmitted independently would lie farther apart (e.g. on different chromosomes) (Schwartz 2008, p. 183). This was a deviation from Mendel's second law and it was Morgan's students who turned this idea into an analytical method. One of his students, Alfred Sturtevant, created the first genetic map in 1913.

The technique to create linkage maps is an extension of simple Mendelian analysis. First, two genes on the same chromosome are selected. Then, their distance is determined by this ratio: Recombinants/Total. After that, other genes are located on the chromosome by measuring their distances to this baseline. The recombination frequency provides the distance once a baseline is established. The frequency of recombinants is determined by the backcross method.

Suppose we are interested in the distance between b and v, two markers on the same chromosome. We first construct a homozygous stock of double recessive females. Then we make the following cross: bvbvX++++ (male) → F1 (bv++) → b+, +v, bv (gametes) X bv (males) → b+bv & +vbv (recombinants) & bvbv (non-recombinants).[23] Thus, the distance between b and v is b+bv & +vbv/ Total.[24]

[23]There is no recombination in males.

[24]We assume that crossing over rate is homogenous across the chromosome and there are no double crossovers.

Mapping methods solved the technical problems posed by Mendelian formulas. First of all, Mendelian formulas could only deal with a small number of mutants. Linkage maps were indefinitely expandable in the face of new mutants. Mendelian formulas described the genetic composition of an organism as a combination of absence and presence of some factors.[25] Maps reflected transmission rates rather than the gene-morphology relations. They gave a spatial representation of linkage relations, which was totally independent from the combined physiological effects of functionally related genes (Falk 2009, p. 36). In short, a structural/spatial representation of genes was replacing a functional/developmental representation.

Once this distinction between a gene's physiological effects and map position is made, it is easier to track genes by their distances to markers. A marker is a genetic variant that has an observable effect on the phenotype as opposed to its corresponding wild type allele. It might affect the eye-color or eye-shape, etc. Using markers and linkage mapping, it became possible to track the multifactorial basis of complex characters. By these technical advances, the time was ripe for the empirical justification of factor constancy and multiple factor hypothesis. Two case studies - truncate and beaded - will show how Mendelians dealt with such cases without recourse to Castle's factor contamination view.[26]

2.6 Gametic Purity, Factor Constancy and the Multiple Factor Hypothesis

One of the major themes of the debate between geneticists in 1910s was gametic purity. There were clear cut cases of Mendelian segregation and recombination. But there were many more traits which didn't fit Mendelism. In experimental evolution studies, artificial selection of mutant phenotypes is the first step. Selection should lead to populations pure for a trait (.e.g. white eyes). The

[25] This absence-presence scheme is also an invention of William Bateson (Falk 2009).

[26] The case of beaded was solved earlier (1918) than truncate (1920) but it is more preferable to begin with truncate because there was a further complication in beaded: balanced lethality.

assumption in Mendelian research is that a few generations of inbreeding should produce pure lines - homozygous for the trait of interest. This is a reasonable assumption if the trait is tied to a single locus with a few alleles. But as will be discussed in detail, the inheritance of some traits like truncated wings in Drosophila or hooded fur color in rats wasn't that simple. The population wasn't pure, even after tens of generations of selection. The question was this: Can the genes themselves be changing? Can these cases be explained by multiple factors affecting the character?

William Castle was one of the first researchers who applied Mendelian principles to the study of inheritance in mammals. In 1903, he showed that albinism in mice was a recessive Mendelian character (Carlson 1966). He saw the Mendelian principle of segregation - gametic purity - a central tenet of Mendelism but he became doubtful about the perfectness of this principle. His experiments with albino mice had shown ".... that not all albinos bred alike when crossed with the same pigmented stock." (Ibid.). Castle didn't reject purity, he only claimed that it was imperfect.

Later in 1905 he offered a model to explain such cases of imperfect purity: contamination. In that model, unit character pairs contaminated each other in gamete formation. He made an analogy such that:

> The union of maternal and paternal substance in the germ-cells of the cross-bred animal is evidently a fairly intimate one, and the segregation which they undergo when the sexual elements are formed is more like *cutting apart two kinds of differently colored wax fused in adjacent layers of a common lump* [emphasis added]. Work carefully as we will, *traces of one layer are almost certainly to be included in the other*, so that while the two strata retain their identity,*each is slightly modified by their previous union* in a common lump. [Emphasis added] (Castle 1905, p. 205).

From 1908 to 1914, Castle, along with his assistant Phillips, was working on hooded rats. These rats have a black area covering their heads and shoulders, like

a hood. Castle and Phillips' selective breeding work created two strains, a plus race which had wider dark areas than the original hooded stock and a minus race with less dark areas (i.e. confined to the head and shoulders). Further selection in these races was shown to be able to increase hoodedness in the minus race whereas it could reduce hoodedness in the plus race.

In 1914, William E. Castle and Phillips published their results concerning the inheritance pattern of hooded character in rats. The trait followed a Mendelian pattern of inheritance of a recessive autosomal character (p. 23). The character segregated and recombined with the expected 1:3 ratio in F2.

The character was not like paradigmatic cases of Mendelian inheritance in some aspects. Hooded vs not hooded was binary and it was a Mendelian character at this level. But the character also looked as a case of imperfect segregation because:
1) Degree of hoodedness in these "pure" breeding stocks varied to a considerable degree.
2) Selection produced different lines with different degrees of hoodedness. These degrees of hoodedness were also heritable (permanent in Castle's words).
In short, it seemed as if selective breeding was changing the gene itself.

There were two possible interpretations of this phenomenon. An orthodox Mendelian would claim that hooded character was under the control of many genes. One gene that was responsible for the presence of the character explains the Mendelian ratios. Other genes might have been modifiers. Even if the stock was pure for the "chief" (i.e. responsible for the presence, binary) gene, it wasn't pure for modifying (i.e. genes that increase or decrease the magnitude) genes.

Castle and Phillips rejected this explanation because, even if there were many modifying genes affecting the degree of hoodedness, many generations of plus and minus selection must have purified the populations for these modifying genes too. They said, their selection experiments produced a nearly all-black plus race and a

nearly all-white minus race. In these conditions, they expected that these races were pure for modifiers too. If they were pure for modifiers, then selection could have no further effect on the degree of hoodedness (p. 24). In addition, Castle believed that postulating new factors whenever a complexity arises was a symptom of bad science (Carlson 1966). One Mendelian factor plus a certain degree of factor variability would be a better explanation. Thus, they concluded that these results were evidence for a change in the hooded gene itself, rather than the result of the action of multiple genes on the hooded character.

Hermann J. Muller, as every orthodox Mendelian would do, offered a multifactorial explanation. He suggested that the original hooded stock "was probably a hybrid between two races of rather remote relationship" (1914 p. 569). Thus, there was stable genotypic variation, before the selection experiments began. If there are many genes affecting a character and if these genes show variation in a population, selection would produce only purer lines, never reaching absolute purity in a few generations of selective breeding. Muller suggested that a good way to purify a race for multiple characters would be brother-sister mating and criticized Castle and Phillips for not doing this.

Muller emphasized that variation in multiple factors could create a normal distribution:

> …the larger the number of factors (for one character) for which a population is heterogeneous, the more numerous are the possible grades of intensity of this character among the different individuals, but fewer will be the individuals which approach the more extreme grades theoretically possible in such a population (p. 570).

Thus, it would be practically impossible in such a population to obtain a pure line for the character considered. In such a situation, selection or crosses with the wild

type will change the character's mean value, not by changing the chief gene itself but by changing the distribution of modifier genes in the population.[27]

Gene fluctuation and contamination were possible ways to explain the effects of selection on the mean magnitude of a character. Muller in 1914 could only show that there was an alternative multifactorial explanation which was strictly Mendelian. But only in 1917-1918, he and Altenburg were able to save the spirit of Mendelism with concrete evidence and rigorous experimentation. The experiments involved two wing shape characters, truncate and beaded. They led to the experimental demonstration of gametic purity - which was later called factor constancy - and the multifactorial basis of non-Mendelizing traits. Although the beaded case was solved before truncate, we begin with truncate because there was a further complication in the former.

2.7 Truncate and Factor Constancy

Mendelian analysis requires clear segregation of alternative forms of a trait and the constancy of forms across generations. In its simplest form, as exemplified by Mendel's original work, there should be constant and easily distinguishable characters in order for Mendelian hybridization experiments to reach clear cut results. However, Mendelians encountered many characters that did not conform to those models. Castle's hooded rats forced him to doubt one of the most basic principles of Mendelism, namely, the constancy (i.e. stability across generations) and purity (i.e. no blending and no contamination) of gametic factors. Truncate, a wing shape form in Drosophila, caused trouble for Mendelian analysis for similar reasons:

[27] The "chief gene-modifier gene" distinction is hypothesized to explain the Mendelian segregation and the variable degrees of the trait. Chief gene is responsible for the former and modifiers are responsible for the latter.

1) Generations of selection for truncate resulted in a population with at most 90 % truncates. No true breeding truncate stock was created, even after a hundred generations of selection. But the property had an obvious genetic basis because, the progeny produced by inbreeding between truncates gave a much higher ratio of truncates than the progeny produced by inbreeding between the longs (i.e. wild type phenotype), all of which were taken from the 90% truncate-10% normal stock (Morgan et al, 1915, p. 191).

2) Even in the purest truncate stock, there is a high degree of variation in truncation. Truncate didn't look like an easily distinguishable character such as black body color or pink eyes. It showed continuous variation: any degree of truncation was observed in the population.

3) Thus, it was proposed that this "was a case of instability of factors or contamination of allelomorphs" (Ibid.). In other words, it was in line with the case of hoodedness in rats, from which Castle and Phillips had inferred the factor fluctuation/contamination view.

4) Truncate X Truncate crosses gave a 1:1 ratio of truncate and normal but with differing degrees of truncation. If truncate had been a single factor, the next generation would give pure truncates but it didn't give such clear-cut results.

5) Altenburg and Muller (1920) constructed an 88% truncate stock and they speculated that the stock was genetically pure but some environmental factor was preventing the truncate trait from developing. To their surprise, truncates gave much more truncates (with a higher degree of truncation) than normals. Thus the stock was genetically impure. Furthermore, the residual variation that could not be explained by genetic variation should have resulted from unknown external factors.

6) Truncate X Wild type crosses didn't give Mendelian ratios like 3:1. The results such as 168 (normal): 1 (truncate) or 2 (normal): 1 (truncate) were inconclusive. Truncation was also not uniform in truncates.

7) When Altenburg and Muller tried to extract purer truncate from the truncate x wild type F2 generation, they observed that truncate x truncate crosses between individuals taken from F2 gave only 50-60% truncate. The character seemed to be "weakened" by fluctuation or allelomorph mixing in the cross with the wild type.

There were two possible explanations for the problematic features of truncate. According to a strictly Mendelian viewpoint, the character should have a complex genetic basis. A complex genetic basis refers to many genes with different effects on the character: some act as chief factors that determine the presence of the character and others act as modifiers which determine the degree/intensity of the character. Mendelian framework presupposes that these factors can be dissociated by appropriate crosses and their relative positions on chromosomes can be determined. Another basic assumption was that the factors were constant. But the case superficially looked as if it was "irreconcilable with Mendelian principles, or indeed with any theory of fixed and segregating factors" (Altenburg and Muller 1920, p. 1).

According to the alternative viewpoint, namely the gene fluctuation/contamination view of William Castle, the gene for truncate is changing by means of mixing with its allelomorphs, including the wild type factor. So, in fact, there was only one factor that caused truncation and its variability was caused by the variability of the factor itself. Altenburg and Muller presented this view with these words: "

Altenburg and Muller's 1920 paper was aimed at giving a Mendelian explanation. They first give some preliminaries about their methods. There are four linkage groups that correspond to the four chromosomes in Drosophila. But crossing over and random assortment might blur the picture. There is no crossing over in

Drosophila males. This is a great advantage in tracking particular chromosomes because markers in the male chromosomes will pass without any reshuffling. In addition, the blurring effect of assortment is countered by marking every single chromosome of a male. Even if this male is heterozygous for all the markers (and in fact it would better be heterozygous for analytical purposes), suitable crosses will still make it possible to see which chromosome has passed to which offspring.

In addition to the lack of crossing over in males, it would be much easier to track a dominant character than a recessive one. This is necessary in this case because if truncate was recessive, we may not be able to track it when it passes to females where there is crossing over. Fortunately, truncate acts as a dominant when it is with Black (a body color mutation). When black and truncate individuals are crossed to normals, the average grade of truncation is 0.79 while non-black (i.e. gray, or the wild type) truncates give a 0.1 ratio of truncate/normal in F1. The relation truncate and black is interesting that their combination make both characters dominant.

After the preliminary points are set, they begin giving the details of their experimental setup. The truncate male whose chromosomes are to be tracked has the following genetic constitution: I*X/I Y, II*B/II b, III*P/III p. It was crossed with a female with the following genetic composition: I X/ I X, II b/ II b, III p/III p. The master gene for truncate was found to lie on the second chromosome. The progeny that was gray (carrying the paternal 2nd chromosome factor), regardless of their carrying the other two supposed factors (i.e. those on the 1st and 3rd chromosomes) showed some degree of truncation. The other two factors were by themselves insufficient for the production of truncate. However, when they occurred with the 2nd chromosome factor, they significantly increased the average degree of truncation. Thus, they are intensifiers. Altenburg and Muller could also synthesize the original truncate male and show that a similar degree of truncation

is present. The master gene and intensifiers were named according to the chromosomes on which they lie: T2' (the master gene), T1 and T3.

The gray red males of the genetic constitution Y, T2B, T3P should all have the same factors in the 2nd and 3rd chromosomes. But they still show great variation in phenotype. These males were crossed to black and pink (a recessive eye color mutation) females. If variation in the males was genetic (i.e. the genes for truncate were actually fluctuating), we should expect marked differences in truncation for different classes. For instance, a cross between a male with minimal truncation and the female from the control stock should produce markedly different level of truncation from the offspring of a cross between the same female stock and a male with maximal truncation. But there was no difference in the average degree of truncation in the offspring thrown out by the different classes, which still showed dramatic differences in truncation. Thus, there seemed to be no gene fluctuation. Variation must be somatic: different classes of truncation resulted from a nongenetic difference that influences the somatic (body) cells but not the gametes.

Altenburg and Muller considered the possibility that selective breeding might have amplified minute genetic variations produced by gene fluctuations to such a degree that they acted as if they were stable. In other words, it was possible that the variability first created by factor fluctuation or contamination passed a certain threshold and the modified genes began acting like normal Mendelian genes. To test this possibility, they constructed a pure line experiment. The pure line idea belongs to Johannsen. He showed, contra Francis Galton, that if some population is parsed into subpopulations of varying characters and if these subpopulations are inbred (or more correctly self-bred in Johannsen's case since this is possible in plants) they will approach subpopulation mean rather than the population mean. These types, which lie behind the observed variation correspond to different "genotypes", the stable factor combinations, according to Johannsen. In Altenburg and Muller's experimental design, self-breeding is unnecessary because the

genotype can be tracked by multiple markers and selecting certain combinations of them.

Again, gray red males with T2’ and T3’ were selected and crossed with black and pink females, but this time, repeatedly. Although Y, II* and III* could be tracked indefinitely, black-pink stock may provide some recombinants that would distort the results of the pure line experiment. Altenburg and Muller made two arguments against this possibility: 1) black-pink stock is homozygous (i.e. there are no recombinants originating from this stock). 2) Since black-pink stock is not subject to selection, even if some unpredictable recombinants appear in this stock, they will disappear in the long run. So, any change in the selected males would specifically show a change in Y, II* and III*. Hence, it would show the fluctuation in the truncate related genes in the experimental stock. Selection experiment gave a negative result: Low-line (i.e. least truncated) and high-line (i.e. most truncated) stocks (subpopulations) gave nearly the same grade of truncation after generations of selection. Thus, there was no genetic difference between them. In short, variation was not due to variations in the genetic constitutions of the subpopulations, caused by gene fluctuation.

Genes were considered to be constant but variation could not be eliminated in the truncate stock. Thus, some factors (genes) should persist in the heterozygous state. Altenburg and Muller explain this by the sterility or non-viability of the homozygous state for some factors related to truncation. T3’ homozygotes were viable but they had low fertility, T1’ homozygotes were also viable. T2’ homozygotes might be non-viable. The test for the occurrence of T2’/T2’ is crucial here. To test whether T2’ homozygotes were viable, the following cross was made: X/Y T2’B/b, T3’P/p (X) T1’X/X, T2’B/b, P/p. If T2’ could be homozygous, the expected ratio would be 3(gray):1(black). The actual ratio was 48:34, which was converging towards 2:1. This ratio shows that T2’/T2’ is non-viable. The case is very similar to balanced lethality in the beaded stock.

2.8 Beaded: The Mechanism Behind Constant Heterozygosity

Beaded is a mutation that causes wing deformation. Just like truncate, it is a problematic case for Mendelian (factorial) analysis. Morgan isolated this mutation in 1910. After 25 generations of selection, he could obtain a 90% beaded stock. If this stock is allowed to inbreed without selection, beaded frequency and the intensity of beaded diminishes and approaches 0%. There are two possible explanations for this: In a Mendelian analysis, beaded might just be a case of constant heterozygosis due to homozygote lethality (like the yellow mouse case). When there is no selection for the beaded phenotype, the recessive factor for beaded will disappear. In addition, the variability between the beaded individuals should be somatic. If factor (i.e. gene) fluctuation theory is true, then the case can be explained as an instance of regression towards the ancestral condition (i.e. wild type).

Beaded flies show great phenotypic variation such that "some of the beaded individuals being very nearly normal in appearance" (Morgan et al. 1915, p. 195). There is variation among beaded and normals, as well as beaded progeny. Normal flies produced much more normal progeny than beaded flies, thus, the difference was genetic (Muller 1918, p. 425). Hence, Muller concluded, in addition to constant heterozygosis and somatic (non-genetic) variability, "the assumption of multiple factors" should be added.

From this 90% stock a constant breeding stock suddenly and unexpectedly appeared (Schwartz 2008, p. 210). This stock, first identified by Morgan, showed much less phenotypic variability than the 90% stock. Again, there are two possible explanations: In Mendelian theory, the case can be explained if it is accepted that a new mutation has appeared, which prevented the production of wild type individuals. It should be emphasized that this is a further assumption, added to the former assumptions of constant heterozygosis and multiple factors. For the factor fluctuation view, the character can be considered to have been "strengthened" to

such a degree that it has passed a threshold. From this threshold, there is no turning back.

Dexter had performed further studies on beaded, in a truly Mendelian spirit. He had found that both environmental (e.g. drought) and genetic factors affected the variability of the beaded character. His most important finding was that the main gene for beaded was linked to pink eye color and ebony body color, which are markers with distinct phenotypic effects, located on the third chromosome. He also found that there is a modifier (intensifier) factor on the second chromosome. According to Muller (1918), Dexter's studies proved the somatic variability assumption (i.e. variation among beaded individuals is not genetic) and the multiple factor assumption of the Mendelian approach.

However, the other two assumptions, namely, the assumption of constant heterozygosis and a new recessive lethal that prevents a reversion to normal haven't been proved. Thus, the dimensions of the problem have been reduced to two. The other half of the Mendelian solution has been given by Dexter. Muller had to show these:

1) One of the factors for beaded (most probably the main factor for beaded, located in the second chromosome) is lethal when homozygous.
2) There appeared a new recessive lethal factor in the chromosome that carries the wild type (i.e. normal) allele for beaded.

Muller used a very delicate method to solve this problem, dealing with many markers at the same time. Muller's method is an extended application of classical Mendelian analysis and linkage analysis. The essence of these methods is to dissociate distinct effects of complex mutant phenotypes, to map the genetic factors associated with these phenotypic effects and to make recessive and invisible mutations visible. Muller used "the growing assembly of known mutants with clearly identifiable phenotypes to map a far larger class of mutations whose

inheritance was more difficult to track" (Schwartz 2008. p. 202). In truncate, Muller used the absence of crossing over in males for tracking the totality of genes on a certain chromosome. In beaded, a miraculous female fly which contained a crossover suppressor on her third chromosome made the tracking of at least some crucial genes possible.

In the preliminary crosses, 5 markers with visible phenotypic effects were selected on the 3rd chromosome. Flies homozygous for these recessive markers were crossed with a fly from pure beaded stock. The progeny was expected to carry the beaded gene on one of the homologous 3rd chromosomes and the selected markers on the other. Crossover frequencies were as expected for every case except one female fly in the F1 progeny. This F1 female showed no crossing over except for 2 markers. Muller concluded that there must be a crossover suppressor gene on the third chromosome of this fly. This gene was located on the right arm of the 3rd chromosome and its suppressive influence was strongest there. In addition, it only prevented crossover in the heterozygous condition. Muller named this factor Cb'.

The F1 female showed another peculiarity. It didn't give any beaded offspring when crossed to normal males. Did the factor for beaded disappear or is it recessive? Muller made a backcross with the pure beaded stock to see if he can obtain offspring homozygous for both Cb' and Bd (master gene for beaded). To track homozygous progeny with quantitative precision, he used the dominant mutation Df' (deformed). Cb' Bd/Df' was crossed with the F1 female. Normals with regard to Df' would be those homozygous for Cb' and Bd' The result was that, neither Df'/Df' nor Cb' Bd/Cb' Bd homozygotes were viable. Muller explained the results such that Df' and Bd were both lethal when homozygous. This explained why the 90% stock of Morgan was constantly heterozygous. The problem now would be to explain how the pure breeding stock originated. Or more correctly, what was the mechanism that prevented the pure stock from reversion to normal?

Muller suggested that during the selection process of beaded progeny in the 90% population, a new recessive lethal must have arisen. The new lethal must lie on the same chromosome with the wild type allelomorph of beaded (i.e. bd) and the crossover suppressor Cb'. The reason is that, unless the new lethal is linked to the wild type gene; the pure stock would continue producing normal progeny. Cb' must be on the same chromosome because if this wasn't the case, the new lethal might have crossed to the homologous chromosome and we would again observe normal offspring (i.e. normals would be heterozygous for the lethal factor).

In order to test this hypothesis, Muller had to confirm that the existence of the chromosome with bd, Cb' and l (the new lethal). This was achieved by crossing pure beaded flies to non-beaded stock which was homozygous for 5 recessive markers. F1 ratio of beaded to normal was 1:1, indicating that the pure stock was in fact heterozygous. It was now time to determine whether the chromosome with bd also included Cb' and l. A dichaete (another dominant marker) female was crossed to a beaded. In the second cross, it was expected that non-dichaete offspring would be homozygous for Cb'. But there was no such progeny. This indicated that either Cb' or the supposed l was lethal when homozygous. It was demonstrated that this factor wasn't Cb' because this factor was sometimes dissociated from Cb' by crossing over. In addition, the position of this factor was determined (Muller 1918, p. 447).

The mechanism that prevented reversion to normal and suddenly produced a pure stock was named the balanced lethal system. In such a system, two recessive lethals in homologous chromosomes and a crossover suppressor prevent the production of normals. In the beaded case, pure stock's 3rd chromosome composition was Bd Cb'+/bd + l.Through inbreeding, these offspring would be: 1) Bd Cb'+/Bd Cb'+, 2) Bd Cb'+/bd + l, 3) bd + l/ bd + l. First and third type of offspring would die before maturation and the stock would breed true.

It is reasonable to assume that recessive lethal would be eliminated by natural selection. But in the case of beaded, the new recessive lethal was linked to the non-beaded factor. The artificial selection for beaded was achieved by eliminating normals. Since the new lethal did just this, it was selected as a free-rider.

The most critical methodological contribution of studies in balanced lethality was the demonstration of the validity of the genotype conception of heredity. Muller (1917) claims that the preliminary data about beaded was very suitable for factor fluctuation or contamination type explanations. But strictly controlled experiments showed that beaded was a complicated but fully Mendelian character. Factors responsible for the phenomenon were discrete, unchanging, noncontaminating Mendelian units of inheritance which were located on chromosomes. Muller goes further and states that cases that apparently contradict with Mendelian models shouldn't be taken as evidence for the views like "... factor inconstancy until factorial analyses of a similar rigorous character have proved such an interpretation to be correct" (p. 625).

The cases of beaded and truncate empirically showed that factor constancy along with multifactorial inheritance could explain at least some complex traits. Mendelian genetics had reached beyond simple binary characters to less clear cases. Muller's approach to extend Mendelian analysis from clearcut cases of factor segregation to less clear cases seemed to be working. But the question about the nature of those inherited units was still not decided upon conclusively. Factors are constant and their combinations produce variation, but what are those factors? The nature of genes was still an open question.

2.9 What is a Gene in Mendelian Genetics?

In 1909, Johannsen had refused to speculate on the nature of the gene. Twenty years later, E. M. East was still skeptical on whether genes are real entities still waiting to be discovered by observation. He had good reasons to be skeptical, because

Mendelian hybridization experiments were not the suitable sort of things that would reveal the structure of genes. Genetic analysis was at the highest functional level (distinct phenotypic characters) whereas scientists like Hermann J. Muller were jumping to the lowest structural level (i.e. molecular structure) from the findings of this functional level.

For East (1929), genes were just useful abstractions for interpreting numerical crossover data. They were shown to reside on the chromosomes. There were many to many relations between genes and phenotypes. But crossover values could be interpreted in different ways. For instance, crossover data could mean a new mutation has occurred or that recombination of existing genes led to a new phenotype. This type of data doesn't allow one to uncover the physical nature of the gene.

For Morgan, the physical structure of genes didn't matter in genetic analysis. Genetic analysis was concerned with markers and the statistical relations of their transmission, not their physicochemical structure. Morgan was tentative with respect to the units of inheritance because he didn't want to go beyond what was provable by experiment. He had a distaste for speculative theories such as Weissman's and struggled to dissociate Mendelian genetics from them. He stated that such theories attributed arbitrary properties to the units of inheritance (Morgan 1919, p. 235).

For Morgan, essence of Mendelism is that there are distinct units of inheritance which segregate in gamete formation and recombine in zygote formation, without losing their identities in the process. Mendelian theory explains/predicts the distribution of traits in the secondary cross by appealing to that essential assumptions. Another essential thesis (Mendel's second law) is that if there are two or more character pairs, their assortment in hybridization (i.e. crossing) is independent. Thus, the germ plasm consists of different pairs of particles which separate and recombine in predictable ratios. Observed ratios can deviate from expected ones mostly because of the phenomenon of linkage. Linkage studies had shown that genes are on the chromosomes and are arranged in a linear order. They are exchanged in the process

of crossing over. Mutations can produce new genes. As of 1919, Morgan believed that experimental evidence is not conclusive on the chemical nature of the gene.

Seven years later, Morgan summarized Mendelian theory of the gene in these sentences:

> The theory states that the characters of the individual are referable to paired elements (genes) in the germinal material that are held together in a definite number of linkage groups; it states that the members of each pair of genes separate when the germ-cells mature in accordance with Mendel's first law, and in consequence each germ cell comes to contain one set only: it states that the members belonging to different linkage groups assort independently in accordance with Mendel's second law; it states that an orderly interchange – crossing-over – also takes place, at times, between the elements in corresponding linkage groups; and it states that the frequency of crossing-over furnishes evidence of the linear order of the elements in each linkage group and of the relative position of the elements with respect to each other (Morgan 1926, p 25).

Evidence had grown but apparently, Morgan still preferred not to say much about the structure of genes. One relevant question was the physical basis of gene constancy. Genes are fairly stable, otherwise, Mendelian analysis would be impossible. What is the underlying physical basis of gene constancy? One plausible answer is that gene is constant because it is an organic molecule. Another is that it is a quantity which fluctuates around a certain mode. First hypothesis is better for Morgan because the second necessitates mysterious forces to explain the constancy of genes in crossing or other transfer phenomena. In addition to this, methodologically speaking, "this is the simplest assumption that one can make at present, and since this view is consistent with all that is known about the stability of the gene it seems, at least, a good working hypothesis" (Ibid. p. 321). But Morgan adds that both hypotheses are equivalent with respect to observed ratios in Mendelian experiments.

He didn't change his stance even in 1934. In his Nobel lecture, he emphasized the inadequacy of the genetic method on the problem of gene structure:

> Now that we locate [the genes] in the chromosomes are we justified in regarding them as material units; as chemical bodies of a higher order than

> molecules? Frankly, these are questions with which the working geneticist has not much concerned himself, except now and then to speculate as to the nature of postulated elements. There is no consensus of opinion amongst geneticists as to what genes are – whether they are real or purely fictitious – because at the level at which the genetic experiments lie, it does not make the slightest difference whether the gene is a hypothetical unit, or whether the gene is a material particle (Morgan 1934).

Hermann Muller was never in good terms with his mentor's tentative way of thinking (Schwartz 2009). He wanted to see what could be inferred from genetic analysis with respect to gene structure. He was also a critique of preformationism - like Morgan - even in his undergraduate years, but he did not see the faults of unit character theory as an obstacle against speculating about the nature of genes. Like Johannsen and Morgan, he knew that genes were distinct from the characters they influenced and complex interactions between genes was necessary to explain development. But still, he thought the nature of the gene is as a legitimate scientific question as anything else.

Muller published his first scientific article on the nature of genes in 1921.[28] There he claimed that genes were ultramicroscopic particles (Muller 1922).[29] They shape the organism by "determining the nature of all cell substances" (p. 32). Muller made a distinction between genes and their effects. The real vital functions might consist of enzymatic action, but this doesn't mean that genes are enzymes (p. 33).[30] In addition, genes act in a network style in the production of visible characters.

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[28] Muller had already shared his opinions on the nature of genes in 1919 but the occasion was an informal gathering of a student club in Columbia. The 1921 speech was given in a top class conference of American geneticists (i.e. American Society of Naturalists) where H. J. Muller was the only person who made bold speculations as discussed below. It was later published in 1922.

[29] An ultramicroscopic particle is a particle that can't be seen with a microscope. The term doesn't specify whether the structure is a single molecule or a higher order structure such as a macromolecule.

[30] This point is of extreme importance if we consider the common opinion of biochemists that genes must be proteins, in order to be the carriers of hereditary information. Muller's functionalist outlook

Muller supposed that the most important property of genes is their ability to replicate themselves. In this replication, raw material is supplied by the cytoplasm. Gene directs the reactions that produce its copy (p. 33). According to Muller, the more interesting phenomenon about genes is their ability to replicate their errors (i.e. mutations). In other words, even if a gene's structure and the resulting organismal phenotype are transformed by a mutation, its ability to replicate itself is left intact.

Bateson, in the same meeting, had defined the essence of evolution as *inheritance and variation*. Muller, directly targeting Bateson's words, suggested that the real essence of evolution is the *inheritance of variation*. Variation is produced by mutations and replicating mutations is the driving force behind evolution. This replication of mutations through inheritance is the theoretical basis of Muller's ideas on the nature of genes.[31]

Muller differentiates his idea from the view that "the autocatalytic mechanism resides in the structure of the genes themselves" (p. 35).[32] So, he doesn't believe in the idea that genes direct each and every reaction in the production of their copies. This is important because this flexible thought allows for a separation between genes and the copying (i.e. the replication machinery) mechanism. He adds the following important remark:

> In either case [i.e. genes directly synthesize their copies or they use a different mechanism, author's note], the question as to what the general principle of

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on genes allows for any type of macromolecule to be a candidate for being the physical realizer of genetic information if it has the power of autocatalysis.

[31] A popular science writer, Richard Dawkins, has popularized the idea that genes are the real units of natural selection. A unit of natural selection, in its simplest sense, is a thing that is "selected for" its effects in natural selection. The origin of this genocentric view of selection is Hermann J. Muller.

[32] Autocatalysis may be considered the progenitor of the self-replication concept. But concepts, while in their infancy, don't have the same meanings we associate with them today. Muller, as I said, borrowed this term from Troland (1917). Troland defined autocatalysis in these words: "the presence of a catalyzer in a chemical mixture favours the production of the catalyzer itself is known as *autocatalysis*".

> gene construction is, that permits this phenomenon of mutable autocatalysis, is the most fundamental question of genetics (p. 35).

The case of mutable autocatalysis is important because Muller interprets it as the enabling cause of evolution by means of natural selection. Inheritance of variation guarantees evolution and "accumulation, competition and selective spreading of the self propagated variations" would mark a distinction between the living and the inorganic worlds: "There would thus result a wide gap between this matter, which would keep growing wider, with the increasing complexity, diversity and so called 'adaptation' of the selected mutable material" (p. 35).

The constancy of genes was already a common assumption of early transmission genetics. But constancy was only an assumption of Mendelian genetic analysis, mostly a methodological assumption as E. M. East interprets it: "A factor not being a biological reality but a descriptive term, must be fixed and unchangeable" (Schwartz 2008, p. 201). Nobody in the genetics community seemed to pay attention to the empirical evidence for this constancy or its physical basis, except Muller.

Muller inferred the stability of genes from low mutation rates (pp. 44-45). If mutation occurred only once in an inbreeding population of 10000 individuals, then the corresponding genes must be relatively stable. In 1921, Muller already knew that environmental factors such as temperature could increase this mutation rate. He said mutation was the key to understanding the nature of genes. If one combines these two views, one can conclude that inducing mutations (i.e. increasing mutation rates by external influences) would be a good way to study the nature of genes. But Muller, in 1921, still had doubts on induced mutagenesis as a window into the nature of the gene because:

1) There may be hidden variation in the population (mutations are not induced at all).
2) X rays or toxic mutagens influence the whole organism. Their effects are not specific enough but natural mutations must occur at *specific ultramicroscopic locations*.

For the reasons cited above, Muller in 1921 preferred classical genetic analysis of naturally occurring mutations (p. 46).[33] Only in 1927, when he gathered sufficient data, he could trust in the efficiency of X ray induced mutations in genetic analysis.

To study genes by means of the analysis of mutations, geneticists need to control (increase) the mutation rate. Short wave electromagnetic radiation, especially X rays is suitable for this purpose. Muller, in his 1927 article, reported that he induced real mutations (not merely organism level aberrations) by X rays in *D. melanogaster.* He used high doses of X rays on sperms and observed "the occurrence of true 'gene mutations' in a high proportion of the treated germ cells" (Muller 1927, p. 84).[34] In Muller's experiments, several hundreds of mutants were obtained.

Muller claimed that these mutations were real mutations because they can be traced through three to four generations. "They are (nearly all of them) stable in their inheritance, and behave in the manner of typical Mendelian chromosomal mutant genes found in organisms generally" (p. 84). In addition, previously studied naturally occurring mutations like the white-eyed (and many others) were re-obtained in this study. This is evidence for the validity of using X rays as an artificial inducer of mutagenesis. The results of this influential study showed that:

1) A gene consists of parts. It has a compound structure. This is inferred from the fact that mutations affect only a portion of a gene in a locus - they don't demolish the gene altogether.
2) A gene and its mutated forms are stable under traditional hybridization and selection experiments. Thus, the compound structure does not imply that

[33] But he also suggested that D'Herelle particles (viruses which infect bacteria) might be good tools to study the nature of the gene. D'Herelle particles satisfied Muller's condition of mutable autocatalysis and hance the conditions for being a gene. Since one can not deny their similarity to genes on a priori grounds, it may be possible to to study the genetics of these tiny things to understand the real nature of genetic material: "Hence we can not categorically deny that perhaps we may be able to grind genes in a mortar and cook them in a beaker after all!" (p. 48).

[34] Here I say reported because Muller doesn't provide the data in his *Science* article.

genes have parts that can be reshuffled. In short, a gene has a *compound* structure with respect to mutability, but it is a *unit* with respect to its transmission.

X ray induction of mutations was still a very crude method to study the nature of the gene. It was not specific enough. X rays influenced many positions on a chromosome at once. But X rays increased the mutation rates. More mutations meant deeper mapping of genes by means of Mendelian genetic analysis. A still more direct approach was required in order to understand the structure and function of the genetic material. This more direct approach is the molecular biology of the gene.

Molecular biology of the gene required a change in model organisms. .*Neurospora* (an ascomycete=a fungus), *E. coli* (a kind of bacterium) and bacteriophages (viruses that infect bacteria) became the main model organisms. One result of studying microorganisms was the one gene-one enzyme hypothesis. It is one of the bridges between classical genetics and molecular genetics.

2.10 The "One Gene-One Enzyme" Hypothesis

In classical genetics, genes are markers for phenotypic differences. But genes are also causally potent entities. How they impose their effects is an important question. At the lowest level, they should be controlling metabolic processes. Metabolic processes consist of chemical reactions. Chemical reactions are catalysed by certain type of protein called enzymes. So, enzymes is a reasonable place to search for gene action.

The studies we considered so far were performed with mostly morphological traits. Genetic study of physiological traits are more difficult because dramatic changes in physiology would most probably be lethal and it is difficult to find easily dissociable character pairs in this domain. But there are exceptions to these facts. Archibald

Garrod's studies on inborn errors of metabolism revealed such Mendelian abnormalities in human physiology.[35]

Garrod was a physician and biochemist, mostly working on diseases caused by the defects in metabolic pathways which can be detected by chemical examination of the contents of urine. His work is considered to be the precursor of Beadle and Tatum's one gene-one enzyme hypothesis:

> … I myself am convinced that the one gene–one enzyme concept was the product of gradual evolution beginning with Garrod…In this long, roundabout way, first in Drosophila and then in Neurospora, we had rediscovered what Garrod had seen so clearly so many years before. By now we knew of his work and were aware that we had added little if anything new in principle.… Thus we were able to demonstrate that what Garrod had shown for a few genes and a few chemical reactions in man was true for many genes and many reactions in Neurospora"(Beadle 1958, quoted in Piro et al. 2010).

In 1902, Garrod discovered an anomaly in infants which was characterized by the blackening of urine upon exposure to oxygen (Garrod 1902). The anomaly is called alkaptonuria. It was not a health concern but there was something peculiar about it. Babies with alkaptonuria were mostly born out of first cousin marriages (Ibid. p. 1617). The pattern of transmission was similar to an autosomal recessive character. But the data was not conclusive because back in 1900s, the medical records were incomplete.

Garrod believed that the anomaly was caused by a defect in a certain step in the tyrosine metabolism. More specifically, the pathway is stuck at the step where homogentisic acid is produced. Since Garrod and the biochemists of the early 20th century knew that these reactions were catalyzed by specific enzymes, Garrod concluded that the error was caused by the lack of a specific enzyme.

[35] In fact, Lucien Cuénot had offered an exactly similar explanation for pigmentation mutants in mice in 1902 but he had to abandon his studies because of the first world war. (Hickman and Cairns 2003).

Alkaptonuria is only one of the inborn errors of metabolism. These traits are monogenic anomalies that concern some metabolic reaction.[36] It's pretty clear why they are called errors of metabolism: they are defects in specific steps of metabolic reaction pathways. The term "inborn", however, must be qualified. It is different from "congenital" such that a congenital defect need not be heritable, it might have been caused by some external factor (e.g. infection) in the uterus.

The error phenotype should be distinguishably different from the normal phenotype and the difference must be constant, just like Mendel's "constant differentiating characters". Continuously varying traits, or traits whose manifestation requires many years, won't count as inborn errors. With respect to this criterion, diabetes or gout are not inborn errors of metabolism, even if they can be detected from the abnormal content of a patient's urine. So, inborn errors of metabolism are metabolic defects that follow a *Mendelian pattern of inheritance*. They are "the chemical analogues of structural malformations" (Garrod 1923, p. 10). Inborn errors of metabolism are in the same class as Daltonism (i.e. color blindness) and night blindness (p. 11).

Garrod believed that, inborn errors of metabolism must be much more frequent than reported cases. In the second edition of his book, he could cite only seven such errors (Ibid.). But this can be explained by the assumption that the defect in the observed function may be much more manifest and complex than its cause, so as to overshadow the simplicity of the cause. The cause might be a simple and little deformation in an organ, or similarly a step in a biochemical pathway, but its manifestation might be large and complex. Garrod gives the example of Waltzing mouse. Waltzing (i.e. pathological repetitive revolving around a fixed point) is an inherited disorder, since selective inbreeding produced a pure line of waltzing mice. The behavior is so strange and so complex that one might doubt its cause is also complex. But the inherited trait is a simple defect in the semicircular canal. The reductive assumption behind

[36] At this point I don't call them diseases because as alkaptonuria case shows, they don't necessarily involve detrimental consequences.

Garrod's thinking is this: "In the same way beneath each chemical sport there may possibly exist some abnormality of structure, so slight that it has hitherto escaped detection" (Ibid. p. 12).

Garrod said that the error would be transmitted as a recessive autosomal factor if it was caused by an inherited defect that causes the lack of an enzyme in tyrosine metabolism. This was the key to Beadle and Tatum's one gene-one enzyme hypothesis. But Garrod's work didn't become an active research program for a handful of reasons. Firstly, humans were not suitable for biochemical analysis, with the techniques then available (Morange 1998).Apart from that, biochemistry of amino acid metabolism required the invention of chromatography and radioactive markers in order to track the intermediate products in each step.[37]Another reason is that genetics and especially population genetics was not developed enough. Especially for human genetics, data was sparse. To study the Mendelian inheritance of characters (whether errors or else), one needs a large set of data on mutations. To see the real power of Mendelian analysis, mutations and the resulting phenotypes shouldn't be too rare to be detected. The reason is that, Mendelian ratios are trustworthy only in large data sets.

Even if the number of known mutations was also low in model organisms like Drosophila, it was possible to make them visible by large scale hybridization and selection.[38] But it was impossible with humans. In addition, healthcare professionals didn't collect their data with a Mendelian spirit, paying attention to consanguinity and other inheritance related factors. This is why, the one gene-one enzyme hypothesis could be fleshed out in the genetic and biochemical analysis of a model organism, namely, *Neurospora*.

[37] The whole biochemical pathway of tyrosine metabolism could be deciphered in 1959 (Ibid.p. 21).
[38] The number of known mutants in *Drosophila* was much higher than humans but still small compared to our contemporary knowledge.

George Beadle began his genetic studies in 1930s with *Drosophila*. He, along with Boris Ephrussi, studied "the genetic and physiological basis of eye colors of *Drosophila*" (Davis 2000, p. 4). In 1937, Beadle began working on the same topic in Stanford University with Edward Tatum. Tatum's lecture on the genetic diversity of microorganisms with respect to nutritional requirements attracted his attention on the possibility of carrying out genetic studies within a certain microbial species. The species in his mind was *Neurospora.* It was a kind of fungus that could easily be raised in petri dishes. More importantly, nutritional requirements of individuals revealed their genetic makeup.

Nutritional requirements of microorganisms depend on what enzymes they can synthesize. A microorganism that lacks a certain enzyme will require the product of that enzyme in order to proliferate. The absence of an enzyme is caused by mutations. So, the specific requirement of a certain colony of individuals shows what genetic defect they carry.

In 1941, Beadle and Tatum published the first paper on *Neurospora* biochemical genetics. The paper is one of the founding documents of molecular biology. In this paper, they emphasized that earlier studies in physiological genetics began with a known trait and aimed at discovering the biochemical basis of that trait. But those already known traits were superficial and too complex to be analyzed biochemically. They were superficial because only nonlethal genetic variants could be studied. For instance, eye color in Drosophila was one of the best studied traits but mutations that affect this trait certainly could not give much information about basic, vital biochemical processes that make an organism develop and survive.Mutations in more basic organic processes would be lethal and hence could not be studied further.

These traits were mostly visible morphological characters whose biochemical basis was intractable in 1940s - hence the complexity. To overcome these defects, Beadle and Tatum reversed the order: begin with known biochemical pathways and learn how genes control those pathways (Beadle and Tatum 1941, p. 500).

Beadle and Tatum exposed *Neurospora* to X-ray radiation in order to create mutants. Some of these mutants couldn't synthesize some necessary nutrients such as vitamin B6. The mutations were lethal if the medium doesn't include B6. But the mutants will live in a medium that includes it. Hence, mutant strains deficient for a specific biochemical reaction could be maintained. By these methods, they identified three specific strains which were deficient for a single nutrient.All of these strains were considered to lack one functional gene. So, a one-to-one relation between a mutant and a biochemical defect was established. But Beadle and Tatum were not clear on the question of whether genes controlled the production of enzymes or they were enzymes themselves:

> From the standpoint of physiological genetics the development and functioning of an organism consist essentially of an integrated system of chemical reactions controlled in some manner by genes. It is entirely tenable to suppose that these genes which are themselves a part of the system, control or regulate specific reactions in the system *either by acting directly as enzymes or by determining the specificities of enzymes* [emphasis added]. (Ibid. p. 499)

Later, till 1945, many more specific defects in metabolism were discovered and a firm theoretical structure was emerging with respect to the following questions:

a) What is a gene at the level of biochemistry?
b) What does a gene do at the level of biochemistry?

With respect to the first question, Beadle (1945a) makes a distinction between the viewpoints of pure genetics and biochemical genetics. For a geneticist, "genes are units of inheritance, carried in chromosomes which correspond to the linkage groups of the geneticist" (Ibid. p. 17). But for a biochemical geneticist, the gene is defined by its chemical composition and its function. As of 1945, Beadle believed that genes were either proteins or nucleoproteins.

With respect to the second question, a geneticist deals with observable differences in phenotypes and their patterns of transmission. But a biochemical geneticist goes further downstream. Every gene has a specific role in the control of biochemical

processes. At the highest level of abstraction, a gene has two types of functions: autocatalysis and heterocatalysis. Autocatalysis and heterocatalysis refer to the gene's role in the synthesis of its own copies and its role in the synthesis of other molecules, respectively. The one gene-one enzyme hypothesis is a thesis about heterocatalysis. A gene's primary heterocatalytic function is to determine enzyme specificities: "Each of these thousands of gene types has, in general, a unique specificity. This means that a given enzyme will usually have its final specificity set by one and only one gene." (Ibid. p. 19). So, the one gene-one enzyme hypothesis says that the primary biochemical function of genes is to determine the specificity of enzymes. "Determination of enzyme specificity", however, was still an ambiguous concept because what makes an enzyme specific and how genes determine this, was not described precisely. All that was known was that each enzyme catalyzes a specific step in a biochemical pathway and there are specific mutations that block each such step.

Schematically, a chemical reaction pathway can be represented like this:

A --->B--->C--->D… Each letter corresponds to a specific molecule and arrows represent the chemical transformation of one molecule to another. Each transformation (i.e. reaction) is catalyzed by a specific enzyme. Specific mutations block these reactions at specific points. For instance, albinism is caused by a mutation that blocks the transformation of 3,4-dihydroxyphenylalanine to melanin, alkaptonuria is caused by a mutation that inhibits the transformation of homogentisic acid to acetoacetic acid, etc. Thus, the original hypothesis was in fact the "one gene-one reaction hypothesis" (Ibid, p. 27).

In this biochemical-genetic model, the relation between genes and enzymes is such that each gene *controls a chemical reaction by controlling the activity of an enzyme*. But the exact mechanism of this control - whether genes produce enzymes or they contribute to the activity of enzymes, etc. - was not known in 1945. However, Beadle's analogy of antigen specificity is suggestive about his views (Olby 1974). In 1940s, it was already known that an antibody's specificity to an antigen was the result

of a fit between two three dimensional structures, like that of a lock and a key. In another paper published in 1945, Beadle stated that "the gene's primary and possibly sole function is in directing the *final configurations of protein molecules* [Emphasis added]" (Beadle 1945b). The final configuration of proteins probably meant the three dimensional structure of a functional protein and the gene somehow determined this structure. But Beadle added that "Such a view does not mean that genes directly 'make' proteins" (Ibid.). The biochemical relations that produce an amino acid required many enzymes so, hundreds of enzymes must be involved in the production of a protein, which is composed of many amino acids. Since a gene is responsible for determining the specificity of one enzyme, there must be hundreds of genes which take part in the production of a protein (Ibid.).

The one gene-one enzyme (or one polypeptide) hypothesis with its modern meaning, could emerge only after it was understood that the proper relation between a gene and an enzyme - or any other kind of protein - is *coding*. The idea that a gene codes for a protein means that the structure of a gene - its specificity in the old jargon - is translated into the structure of a protein, namely, its primary structure. The "genetic code" idea is one of the most productive simplifying assumptions that has ever been invented in biology.[39] The biochemist's (Beadle 1945b) vision implied that each and every step in protein synthesis had equal explanatory weight. But in the coding idea this complex biochemical machinery fades into the background and one and only one relation gains salience: the relation between sequences. The unit of inheritance - the gene - becomes the bearer of information that specifies a functional protein.

2.11 Conclusion

Mendelian genetics could take of the ground - turn into a fertile research program - because of certain simplifications. Firstly, inheritance was separated from

[39] The coding idea is comparable to Darwin's natural selection in this respect. Natural selection and the genetic code ideas reduce the complexity of their respective objects of knowledge and unify diverse phenomena. The capacity of the coding idea with respect to guiding research will be discussed in the next chapter.

development and evolution: transmission became the sole focus of attention. In Mendel's experiments, the ratios of different forms of a character were traced. In Morgan and his students' early research, map positions inferred from recombination ratios were the focus, rather than the physiological action of alleles in development.

Secondly, the choice of model organism and traits involved a further simplification. Mendel's garden pea (*Pisum sativum*), Morgan's fruit fly (*Drosophila melanogaster*) and Beadle's bread mold (*Neurospora*) were easy to handle and did not cause complications encountered in species such as *Hieracium.* The characters Mendelians studied usually followed a simple pattern of inheritance and they were observable. The third simplification, or methodological rule of thumb, frequently used by Mendelians was that more complex characters - apparently non-Mendelian ones - could be analyzed by the same methods that applied to paradigmatic cases. For some workers in the field, such as William Castle and John C. Phillips, traits that didn't fit Mendel's principles should be handled by loosening those principles (i.e. gametic purity). For another critic of Mendelism, Wilhelm Johannsen, the hereditary basis of species-typical, basic traits could not be studied in the Mendelian framework. He had claimed that Mendel's laws were applicable to a tiny set of superficial characters. But Mendelians chose to attack those complicated cases with the methods that they knew to have worked well in simpler cases. At first, they hypothesized that complex traits had a multifactorial genetic basis. Then, they showed this experimentally, in problematic cases such as truncate and beaded. The resolution of these two cases was made possible by the rule of thumb mentioned above: if the trait is non-Mendelian, make it Mendelian by dissecting its genetic basis into distinct factors. By this way, Mendel's principles which were originally (1865) stated for "constant differentiating characters" were being extended to much more complicated cases.

In this process, the theoretical framework about gene action was also improved. The simple unit character view was replaced by many to many relations between gene variants and phenotypes. In addition, the nature of the unit of inheritance - the gene - seemed to be within reach, at least for pioneers like Hermann Muller. He

hypothesized that the gene was an ultramicroscopic particle that has the capacity of mutable autocatalysis. He based Darwinian natural selection on this capacity. A new, gene-centric vision of biology was culminating.

However, all that could be studied in the Mendelian framework was still those traits with few known alleles at their genetic basis and the researcher was bound by whatever mutations Mother Nature provided. Neither the nature of genes nor their biochemical functions could directly be studied.

In 1927, Hermann Muller published his results concerning X-ray induced mutants in Drosophila. According to that short report, X-rays could immensely increase the rate of mutations. Increasing the rate of mutation meant that genetical analysis could go much deeper. An increase in the number of mutations would lead to better resolution in linkage mapping and a deeper understanding of gene function. To see the real capacity of induced mutations for genetics, researchers had to move onto a different model organism. In 1940s, George Beadle and Edward Tatum studied the effects of induced mutations on the biochemical machinery of red bread mold *Neurospora crassa*. Their findings indicated that each gene controlled a single step in a metabolic pathway. Gene action was being transformed into a problem that can be attacked with the tools of biochemical genetics. Soon, the structure of the genetic material would be uncovered. The emerging theoretical framework for gene structure and function was an informational one.

CHAPTER 3

MOLECULAR BIOLOGY OF THE GENE: THE INFORMATIONAL FRAMEWORK

3.1 Introduction

Mendelian genetic analysis dealt only indirectly with genes. The real focus was on the transmission pattern of phenotypic differences.The nature of the gene and the mechanism of gene action became a direct object of study only with the advent of molecular biology.[40] Emergence of molecular biology provided more direct means to study gene structure and function.

Molecular biology is the study of life at the molecular level.[41] Molecular level consists of macromolecules, their specific structures and their chemical interactions. The aim of molecular biological research is to discover molecular mechanisms that produce the peculiar characteristics of organisms, such as reproduction, metabolism, development and evolution.

The period between 1940 and 1960 is the founding era of molecular biology. In that period, DNA double helix structure was discovered (1953), the first protein (insulin) was sequenced (1949-1955), first 3D model of a protein was built, coding problem emerged, the operon model of genetic regulation was proposed (1958-1961), transfer

[40] Here, the word "direct" is used in a loose manner so as to indicate the difference between the genetic study of genes in which genes are inferred from gross phenotypic differences and the structural study of DNA in biophysics or the biochemical study of DNA replication and protein synthesis. Direct/indirect distinction is relative.

[41] The term "molecular biology" first appeared in 1938, in a document written by Warren Weaver (Sarkar 2006). Weaver was the director of Rockefeller Foundation's Natural Science Division and an influential scientist in the making of United States' science policy. Rockefeller foundation had a great interest in molecular biology and they funded researchers including Jacques Monod, Linus Pauling, Theodosius Dobzhansky, Max Delbrück and T. H. Morgan among many others (Kay 1993).

RNA was discovered (Judson 1996). Here I list only the major discoveries; the ones that paved the way for them are omitted. Molecularization of biology amounts to "the change in character of acceptable explanations" or more correctly to "a change in the ruling way of framing hypotheses in biology" (Ibid, p.178). Problems had to be workable with the tools of molecular biology and hypotheses should be testable by the same tools.[42]

Information became a key concept in molecular biology through the studies on the genetic code and bacterial genetic regulation. The gene of Mendelian genetics was merely a marker for heritable phenotypic differences, which obeyed Mendel's laws in its transmission. In the molecular era, the gene was transformed into an information bearer as well as an information processor.

In this chapter, key concepts of molecular biology will be examined in the context they appeared in history. Those concepts are specificity, information and regulation.

3.2 Biophysical Reduction and Molecular Biology: General Laws vs. Specific Structures

Molecular biology is an experimental science with a reductionist orientation. By reductionistic, I mean a preference to explain wholes by means of parts and their interactions. In other words, it is a preference to explain a higher level property by means of the properties of entities at a lower level. Here, higher-lower distinction is equivalent to the whole-part distinction. It is important to keep in mind that reduction does not necessitate explanations at the lowest level, such as particle physics. A layer-cake model of reduction is more appropriate here. In such a model, to reduce a property simply means that it is explained at a *lower* level, not the lowest level possible (Brandon 1996).

The theoretical origins of physicochemical reduction of biological phenomena can be

[42] Some of these tools will be specified later in this chapter.

traced back to the arguments of mechanists against vitalists. The mechanism-vitalism debate concerned the possibility of explaining organic processes with the methods of physics and chemistry. Vitalists believed that explanation of life required different principles, forces and laws than those of chemistry and physics (Bechtel and Richardson 1998). In other words, they believed that there was a fundamental, qualitative difference between living things and inorganic entities. The distinctive properties of organisms included self-maintenance, regulation, sensibility, development, etc. Vitalists believed that these properties could not be explained by physical and chemical principles. In a sense, they were irreducible properties. Mechanists, on the other hand, believed that the difference was a difference in the degree of complexity (Ibid). Hence, in the mechanistic conception, there is no principled barrier against explaining organic processes within physics and chemistry.

The mechanism-vitalism debate was not a debate between unscientific vitalists and scientifically minded mechanists. From a contemporary perspective, given that vitalism is long dead, vitalists seem to be following a pseudoscientific line of work. But in the 19th and early 20th centuries, there was a real debate about the proper ways of conducting biological research and the interpretation of results of that research. Complex organic phenomena such as development, inheritance, metabolism, could not be explained in the same manner as the trajectory of a cannon ball or the oxidation of coal was explained. Mechanistic biology won because its insistence on the experimental method proved to be progressive. But, in the meantime, mechanistic biology had to be transformed to capture the unique properties of living things.

The mechanism-vitalism debate extended to the 20th century, when biology was becoming an experimental science. Jacques Loeb's *The Mechanistic Conception of Life* was an influential defense of the mechanistic perspective. More central to the topic of this chapter, was Loeb's vision on how biology would become an experimental science, rather than a merely descriptive or speculative one. For Loeb, to become an experimental science, biological research should either gain experimental control over the studied phenomenon - i.e. the researcher should be able

to recreate the phenomenon at will - or that the researcher should find exact numerical relations in the results of his experiments, as Mendel did (Loeb 1912, p.3). Loeb believed that every mysterious phenomenon such as the "activation of the egg cell" after fertilization or heredity, will one day find a physicochemical explanation. Loeb's (1912) explanations are very crude with respect to contemporary standards. For instance, he explained complex processes - such as development - on the basis of enzyme assisted oxidation of nutrients. The specifics of biochemical or genetic processes were not even touched by Loeb's account. Loeb's reductionism was too simple and too general to account for complex processes. As Jacques Monod later observed, molecular biological view of organisms was very different from Loeb style physicochemical reductionism:

> The biologists at that time - and the time is extended into the days when I was a student, so I know quite well - believed, to put it roughly, that the laws of gases would explain the living beings. That is to say, metabolism in the cells would be explained by the general laws of chemistry. (Judson 1996, p. 186).

Molecular biology was different from this perspective because in molecular biology, explanation of a biological property or process depends on specific mechanisms rather than general physicochemical laws. The new way of looking at organisms consisted of such ideas: Macromolecules, their specific structures and their interactions can explain life processes.[43] Some macromolecular mechanisms such as the protein synthesis machinery are simple and universal (Ibid., p. 179). Simplicity here means the mechanism has few components (i.e. DNA, transfer RNA, messenger RNA, ribosomes and a few enzymes) and universality means it is shared by all organisms despite the apparent diversity of life.

This universality should not be confused with the universality sought by early reductionists like Loeb. It isn't a consequence of the universality of physicochemical

[43] A macromolecule is a relatively big molecule composed of several component molecules. For instance, proteins are composed of several amino acids and DNA is composed of several nucleotides. The specific structure of a macromolecule can denote either its 3D shape, along with its overall electromagnetic properties, or its linear sequence.

laws. Rather, it results from the fact that all organisms *evolved from a common ancestor*. Thus, it is the result of a historical contingency, not a physical necessity *per se*.

Another difference between the old reductionism and molecular biological framework was that, in the latter, at least some processes are different from ordinary chemical processes: they are informational. The meaning of information in classical molecular biology has a tight connection to the concept of specificity.

3.3 Structural and Biochemical Senses of Specificity

The concept of information found a fertile ground in molecular biology, through the developments in bacterial genetics, biochemistry and biophysics. At first, before the construction of an explicitly informational terminology, "specificity" was the key term defining the molecular biologist's viewpoint on organic processes (Sarkar 2005, p. 208). Till 1930s, biologists had learnt that biochemical reactions involved specific interactions (Ibid.). Enzymes acted on only one kind of a substrate and antibodies interacted only with their respective antigen types. And this specificity depended on the 3D structures of interactants. For instance, Linus Pauling had suggested that the specific binding of antibodies to their respective antigens depended on the specific configuration of the antibody proteins (Pauling 1940). The specificity of antibody/antigen interactions depended on the *complementarity* of parts of an antigen to the *configuration* of the antibody (Ibid. p. 2643). Later, Pauling would crown specificity as the definitive property of biological substances:

> The most striking and characteristic property of biological substances is the specificity of activity which they show - the power to combine selectively with or to influence the behavior of one substance, rejecting others with a precision and certainty seen in few physical and chemical phenomena (Pauling 1947).

The specificity of biological substances - e.g. enzymes and antibodies - depended on the capacity of each such substance to take alternative configurations. The set of possible configurations were constrained by the free energy level of each

configuration. According to Pauling (1947), specific activity resulted from weak forces (i.e. hydrogen and ionic bonds) between the antibody and the antigen at the surface of each. The binding of antigen changed the configuration of the antibody such that a low energy union was formed. This model - i.e. the induced fit model - he believed, could be generalized to enzyme specificity as well. In short, the specificity of biochemical action was being explained by the specific configurations of certain molecules.

The biochemical genetics of microorganisms, around 1940s, was aimed at identifying the specific genes responsible for the control of what Pauling called "specifically acting substances", especially enzymes. Beadle and Tatum's one gene-one enzyme hypothesis, which was discussed in the previous chapter, stated that genes specifically determined the activity of their corresponding enzymes[44]. The nature of this specificity was not described at the precise structural level yet. But the idea of a one to one connection between genes and enzymes implied that genes and their mutations would have very specific effects at the biochemical level. This was a bold hypothesis for it's time because geneticists, since Johannsen's (1911) genotype-phenotype distinction, were careful in distinguishing the effects of gene substitutions (mutations) from the production of phenotypes.

Prominent Mendelian geneticists such as Morgan and Muller had hesitated to propose direct connections between genes and phenotypes. Muller (1922, p. 32) had emphasized that the production of characters - those studied by Mendelian geneticists - required "a highly complex, intricate, and delicately balanced system of reactions" which made it impossible to build one-to-one connections between genes and phenotypes. Morgan (1926) had claimed that a single gene had manifold effects and multiple genes could influence a single phenotypic property. Neither Morgan nor Muller were referring to biochemical reactions, their point concerned observable morphological characters. At a deeper level than morphology, a gene and its

[44] The original hypothesis was one gene-one reaction hypothesis, as told in the previous chapter.

mutations could still have very direct and specific effects. Archibald Garrod (1923, p. 1), a forerunner of the one gene-one enzyme hypothesis, had stated that behind the seeming *uniformity* of biological structures in a species, there might lie a *diversity*, not observable except at the level of biochemistry. This was Garrod's reductionistic vision of *biochemical individuality*, which implied that subtle interindividual differences in phenotypes should be traced back to differences in the structures of proteins (Ibid, p. 2). Beadle and Tatum's studies weren't suitable for pointing at the structures of proteins or the genes, for they confined their studies to the genetic analysis of the effects of mutations on the nutrient requirements of *Neurospora* strains, rather than a direct structural analysis of genes or the enzymes. The deficiency, however, would soon be compensated.

While experimental biology was moving towards a direct study of gene structure and function, a prominent physicist, Erwin Schrödinger, was contributing to the theoretical foundations of the informational framework. Schrödinger's *What is life* (1951 [1944]) was the first document that compared genetic material to a "code-script", carried in an *aperiodic crystal.*[45] The aperiodic crystal was invoked to answer the following question: How can the tiny chromosomes in a fertilized cell determine the adult form as well as the steps of development, beginning from a single cell and resulting in the multicellular organism? (Schrödinger 1951 [1944], p. 20).[46] In modern day terminology, Schrödinger's question was a question about information storage in a certain physical medium, even if he never used the concept explicitly.

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[45] In 1902, French biologist Lucien Cuénot had termed genes as *mnémon*, derived from the Greek word *mnemonikos*, meaning memory (Hickman and Cairns 2003). It referred to the "inherited entity that holds the memory of how to make something..." (Ibid.)

[46] In fact, this is a deliberate transformation of the problem Schrödinger had in mind. This formulation of the question implies that Schrödinger was dealing with the distinctively biological problem of the genetic control of development, which is essential for our purposes in this chapter. Schrödinger's real aim was to show that even a small number of atoms (e.g. 1000) could form stable/ordered structures (Moss 2003, Olby 1974). This was important because in statistical mechanics, lawful regularities hold only if the number of interacting particles is high. But the quantum mechanical theory of chemical bond would obviate that requirement.

Schrödinger's book was influential in attracting the attention of physicists into the problems of biology. It had brought a fresh outlook on the problems of biology coming from quantum mechanics and statistical thermodynamics. The book was a source of inspiration probably because it showed a way to transform biological problems into problems that were soluble - or at least understandable - by the methods of physics. Crick, a physicist turned molecular biologist, remembered the "feel" of reading Schrödinger such that "...he made it seem as if great things are just around the corner." (Crick 1988, p. 18). Another physicist, who worked in the Manhattan project, Maurice Wilkins, had turned to biology after reading *What is Life* (Judson 1996, p. 77).

Schrödinger's short book was not the only reason physicists turned their eyes on biological problems. In fact, Schrödinger's book had made use of Max Delbrück's model of gene structure. Max Delbrück was a former physicists who worked with Niels Bohr and he was directed to biology by his mentor. Max Delbrück began his studies with the dream of discovering new laws of physics through studying living things (Morange 1998, p. 41).

Delbrück began his career in biology in X-ray induced mutations in Drosophila (Olby 1974, p. 232). In 1935, he, along with physicist Karl Zimmer and geneticist Timoféeff Ressovsky, published a paper on gene mutations and gene structure (Timoféeff-Ressovsky, Zimmer and Delbrück 1935). In that paper, the authors tried to infer the physical properties of genes by means of bombarding them with X-rays and analyzing the mutations produced.

Delbrück knew that the gene was a fairly stable entity because changes in gene structure - mutations - were rare events (Olby 1974). It was a well known fact, even in 1920s that environmental manipulations such as increasing the temperature could increase mutation rates (Schwartz 2008, p. 238). Further, Muller (1927) had shown that X-rays could also increase mutation rates, as much as 145 times higher than the normal rate (Schwartz 2008, p. 239). X-rays or other kinds of short wave radiation, could illuminate why the gene was stable as well as why it changed (Olby 1974, p.

233).

Muller (1922) had previously suggested that the most interesting property of genes is their ability to copy their mutations. Genes were stable but when they change by mutation, the mutant allele was also stable. Thus, Delbrück's question turned to be why the gene is stable and why that stability is not lost after a mutation[47]. In his quantum mechanical model, he stated that gene had a nonrepetitive atomic structure. This might have been the basis of Schrödinger's aperiodic crystal idea. Because an aperiodic crystal, as opposed to a periodic one, was a nonrepetitive structure and this was key to it's carrying the specifications to build an organism. The so called "three man paper" was also providing the first quantum mechanical account of gene stability and mutability: "....the stability of the gene was due to the strength of inter-atomic forces, and its mutation was due to a quantum jump from one stable configuration over the energy 'hump' which separates one configuration from other" (Olby 1974, p. 234)

The authors, albeit incorrectly, derived the average size of a gene as being approximately 1000 atoms. The paper was in line with the target theory, which suggested that the average size of a gene can be estimated from the magnitude of X-ray exposure (measured in Roentgen units), the number of germ cells affected, the average volume of a cell and the increase in the mutation rate (Carlson 1966, p. 158).[48]

The method of inference in the so called target theory resembled "… firing a shotgun shell (of known size) into a swarm of bees (of known density) and estimating, from the reduction in stinging power of the swarm, the diameter of the individual bee

[47] In fact, the gene can be completely destroyed by some types of gross mutations such as deletions, in which case the stability is out of the question. In X-ray mutagenesis, especially in its early applications, resolution was very low: X-rays induced an intractable number of genetic as well as physiological changes, independent of the mutations. It was like cutting a cake with a fire axe.
[48] This is a simplified list of possible variables that should be taken into account. For instance, the duration or frequency of exposure are omitted.

(Judson 1996, p. 35).[49] The reasoning was clever, but the premises were biologically unrealistic.

Muller (1940) identified many incorrect premises in studies that infer the size or structure of the gene from the frequency of mutations induced by radiation. Firstly, a single ionization event, induced by radiation, can cause more than one genetic change, and some of these changes can be at different locations on a chromosome (Muller 1940, p.41). In other words, there is no one to one spatial correspondence between radiation induced ionization and mutation events, as assumed by the followers of target theory. Secondly, not all ionization events lead to mutations. Thirdly, even if every ionization event causes a mutation, the effects of the mutation may not be detected by the methods used in such studies. Lastly, the effects of an ionization event might not be local. In other words, an ionization event in the boundaries of a gene might cause a mutation in another gene.

Target theory, as well as the methods it depended upon, did not prove to be fruitful with regards to the question of gene structure. Delbrück had tried to attack the problem of gene structure from a purely physical angle. Although induced mutagenesis was a fertile approach to study chromosome mechanics or gene function, it was too crude to investigate the structure of the gene. Working with Drosophila was another handicap because Delbrück's aim was to see what made the gene stable and how it replicated, and he wanted to study these phenomena at their purest, quantum mechanical form, as structural chemists like Linus Pauling had done (Olby 1974, p. 235). For such a study, he should at first be able to isolate genes, replicate them to an appreciable quantity and study them in isolation, not in the organismic, cellular and chromosomal contexts they appear. A gene in a multicellular organism is surrounded by other genes, chromosomes, the nucleus, the protoplasm (i.e. the old name of cytoplasm), and other cells, so and so forth. Its effects are mediated, modified

[49] This phrase refers to another study by Salvador Luria on determining the size of individual phages. It is included here because it is one of the best informal expositions of the general logic of target theory. For other good informal expositions, see Carlson (1966, p. 158) and Morange (1998, p. 45).

and obscured by a jungle of causes. The replication of genes in a cell are mediated by the replication of the cell itself. To observe gene replication in the pure form, a simpler system was required. In a sense, Delbrück wanted to turn Muller's dream into a reality: "Hence we can not categorically deny that perhaps we may be able to grind genes in a mortar and cook them in a beaker after all." (Muller 1922, p.48). A special type of virus, bacteriophages, would become his next model organism.

Bacteriophages, phages in short, proved to be a better genetic system to uncover the macromolecular basis of heredity than Drosophila.They had a very simple genetic material and they didn't have any metabolism. They were thought to be pure genes.[50] They reproduced by using the metabolic machinery of their hosts. It was also known that they had mutations. They were too small to be investigated at the level of phenotype - except by electron microscopy. But their capability to infect bacteria showed genetic variation. And similar to *Neurospora*, mutations could be induced by X-rays and other types of high frequency - short wave - radiation.

Delbrück was fascinated by two additional properties of these tiny viruses. First, it was possible to crystallize them and their most essential property, the ability to infect bacteria, is not lost by this process (Olby 1974, p. 236). So, it was possible to investigate their physical properties without caring about the technical constraints brought by the manner of treatment. Even the simplest unicellular organism could not be handled that harshly.

The other property was that they could replicate with enormous pace. A single virus would make 100 copies of itself in 20 minutes (Olby 1974, p. 237). Large numbers are important both in genetic and structural analysis. They make statistical inferences precise and structural analysis secure. As small, simple, mutable, crystallizable and

[50] Genes were thought to be made of protein in the late 1930s, the time at which Delbrück began studying bacteriophages. So, these viruses were at first thought to be pure proteins with the capacity of mutable autocatalysis.

fast replicating "pure genes", phages were very suitable for a direct attack on the genes.[51]

The central target in phage research was to identify how they replicated in the bacterial cells (Ibid). Their genetic makeup made a difference. Genetically different strains of viruses differed with respect to their capacity to infect and kill certain kinds of bacteria. When a colony of bacteria is infected and later killed by phages, a certain circular plaque appears in the petri dish. This was the observed phenotype, from which the genetic differences were inferred.

In 1942, Delbrück and Luria infected bacteria with two genetically different strains of viruses. Their expectation was to see both strains would infect the bacteria, reproduce in it, and would be recovered. But they saw that only one strain could reproduce, and there was no trace of the other. What they saw, in fact, were the plaques created by dead bacteria. If only one kind of virus bursts the bacteria, the plaque is circular but if two kinds burst out, the plaque would be nebulous (Delbrück 1945, p. 153). The plaque was circular, only one strain reproduced and as of 1945, Delbrück called this phenomenon "the mutual exclusion effect" (Ibid. p. 151). This was only one part of the story. Virus strain 1 had excluded virus strain 2 from reproducing, but virus strain 2 had lowered the *rate of reproduction* of the first strain. Delbrück called this the depressor effect. The fact that two kinds of viruses *interacted* in their replication was suggestive of the inadequacy of seeing viruses as pure genes which could be studied in the same manner as simple chemical structures were studied.

Delbrück had wrongly believed that virus reproduction was a simple phenomenon, a phenomenon that wasn't contaminated by any of the complications observed in the sexual reproduction of multicellular organisms such as Drosophila. One source of complication was recombination - the exchange of genes between homologous

[51] Viruses are not pure genes. They are composed of a genetic material - either DNA or RNA - surrounded by a protein coat. This was not known in 1940s.

chromosomes. For a geneticist, recombination was a familiar process. Recombination rates were used in the creation of gene maps in Drosophila. Linkage, which was a deviation from Mendelian principle of independent segregation, had been transformed into a tool to measure the distances between genes on a chromosome. But viruses, the so called "pure genes" of Delbrück were expected to replicate as units, with no recombination and no linkage. In 1948, Alfred Hershey and Raquel Rotman demonstrated that both of these phenomena - recombination and linkage - were observed in viral replication (Hershey and Rotman 1949). Whether the exchange of genes happened by the same mechanism as multicellular organisms, i.e. crossing over, was not certain, but "the existence of some kind of linkage system conditioning segregation and reassortment of genetic factors among viral particles seems quite clear…" (Hershey and Rotman 1948, p. 96). This result showed that virus replication, although simpler than the reproduction of other model organisms, was not a case of pure replication of pure genes - the atoms of heredity.[52]

One year later, Delbrück would describe the discrepancy between organisms and the physicists' approach as such:

> A mature physicist, acquainting himself for the first time with the problems of biology, is puzzled by the circumstance that there are no 'absolute phenomena' in biology….The organism he is working with is not a particular expression of an ideal organism, but one thread in the infinite web of all living forms, all interrelated and all interdependent. The physicist has been reared in a different atmosphere. The materials and the phenomena he works with are the same here and now as they were at all times and as they are on the most distant stars. (Delbrück 1999 [1949], p. 89).

These observations, however, didn't show that a physical approach on genes was futile. They could at most show that a still more structural - as opposed to genetic - approach was needed. One such line of work was being carried out in Linus Pauling's lab in Caltech and Sir William Bragg's and John D. Bernal's labs in Cavendish. They both were studying the structure of molecules by first crystallizing them and then

[52] The genetic analysis of virus mutations and recombination was not a dead end in genetics.

applying X-rays. X-rays scattered by the nucleus of atoms gave a crude 3D picture of the crystallized molecules. Linus Pauling, in 1930s, had discovered the α-helical structure of some proteins (Darden and Tabery 2009). But the question of gene structure could only be answered if scientists knew what type of molecule the genetic material was. It turned out to be deoxyribonucleic acid and it was shown, in 1953, to have a double helical structure (Watson and Crick 1953).[53]

3.4 DNA and Two Concepts of Information

DNA double helix has a very regular and relatively stable structure. Regularity and stability of DNA is provided by its sugar backbone. The essential property, however, is that it is not monotonous - it is aperiodic, in Schrödinger's old terminology. DNA consists of four nucleic acids, which are not ordered in a repetitive manner.[54] This gives DNA the ability to carry genetic information.[55]

The first strict formulation of genetic information was given by Francis Crick. According to the sequence hypothesis, DNA exerted its influence on the organism by determining the sequence of amino acids in proteins. Proteins have a primary role in almost every biological function. Some act as enzymes, others as ion gates, building blocks of the cytoskeleton, etc. So, the set of amino acid sequences in an organism can be considered as the deep phenotype of that organism:

> Biologists should realize that before long we shall have a subject which might be called 'protein taxonomy'-the study of the amino acid sequences of the proteins of an organism and the comparison of them between species. It can

[53] The history of this discovery has been told in so much detail that no repetition is intended in this chapter. Olby (1974, Section 5), Judson (1996, Part 1), Crick (1988, chapters 4-6) and Watson (1968) are the best sources on the topic.

[54] There are repetitive nucleotides in eukaryotic genome but they don't code for proteins. They have other functions.

[55] To understand the difference, suppose we have a repetitive sequence of adenines (a nucleic acid). AAAAAA… would be compressible into the string *Axn* where *n* is the number of repeats. Hence,a knowledge of the full sequence is unnecessary: it can be inferred by knowing only one of its constituents. But a sequence like TACTGC… is not redundant, it carries more information.

> be argued that *these sequences are the most delicate expression possible of the phenotype of an organism* [Emphasis added.] and that vast amounts of evolutionary information may be hidden away within them. (Crick 1958, p. 142).

As of 1958, Crick had formulated another important principle: the central dogma of molecular biology.[56] According to the central dogma, information flows from nucleic acids (DNA and RNA) to nucleic acids and proteins but not from proteins to proteins or proteins to nucleic acids. This, Crick believed, was a restatement of non-inheritance of acquired characteristics at the molecular level (Sarkar 2005). Information, according to Crick, is "the precise determination of sequence". So the dogma says nucleic acids can precisely determine the sequence of amino acids of other nucleic acids and proteins but proteins can't determine the sequence of nucleic acids or proteins. The word "precise" is immensely important here because proteins can crudely determine the sequence of other proteins and nucleic acids. For instance digestion enzymes and restriction enzymes can cut proteins and nucleic acids into pieces respectively, hence, they can determine the amino acid sequence of proteins, albeit in a crude manner. Precise determination means that only nucleic acids (DNA or RNA) can determine the letter-by-letter sequence of nucleic acids and proteins.

The sensitivity of the organism to external and internal non-genetic clues will give us the second concept of information. Let's call it, for now, information as regulation. An external clue becomes a piece of information only for an organism that has the mechanisms to translate it into some adaptive response. So, here, the informational framework is extended from static sequences into networks of interactions between genes, regulatory proteins and signalling molecules.

[56] The central dogma was first formulated in October 1956, in an earlier, unpublished draft (Crick 1956). The draft can be found in this URL: https://profiles.nlm.nih.gov/SC/B/B/F/T/_/scbbft.pdf

These two informational concepts will be described in the historical context they emerged. They are tied to two problems of biology: the problem of genetic code and the problem of regulation of metabolism in bacteria.[57]

3.5 The Path to the Genetic Code[58]

Francis Crick claims that after the structure of DNA was discovered in 1953 and the first protein amino acid sequence was discovered by Sanger in 1955, it was clear for him that the next target was to find the rules by which DNA sequence determined the amino acid sequence of proteins (1988, p. 89). But in fact, the path from DNA to protein proved much more complicated than first expected. To understand the coding problem and how it was solved, we should first understand the prerequisites for formulating and solving the problem. In other words, we should understand what was lacking before 1966, when the code was completely solved. More importantly, we should understand which false theoretical assumptions had to be overcome, in order to make new hypotheses look more tenable.

In first half of twentieth century, biochemists believed most polymers had repetitive structures. They were in search for chemical rules for the assembly of polymers. This

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[57] The solution of these puzzles relied heavily on the discoveries and conceptual changes already covered in the sections above. For this reason, upcoming sections will repeat some content, but in the specific context of the problems mentioned.

[58] The word "path" can be interpreted as suggesting a linear pattern of scientific progress towards a preordained goal. In the historical reconstruction of a scientific discovery, one has to begin with the discovery itself and then reach out to the prerequisites of that discovery. Let me call the discovery the *target* and its prerequisites the *source*. The method of backwards reconstruction enforces a bias in the assignment of explanatory weight to the set of relevant knowledge in a given field in a given period; this is inevitable and legitimate. Some sources are weighed more heavily than others because they have a more direct connection to the target. To overcome the illusion of preordainment, one should consider what alternative paths might have reasonably been followed. Robert Olby (1994) did this by presenting failed theories (colloidal theory) in an objective fashion and Carlson (1966) did it by telling us the merits of the "target theory". More radically objective histories can be written only if we abandon the source-target model of history - e.g. we focus on the studies made in a specific laboratory - but this time, I suspect, we will lose the significance of discoveries towards the progress of science. I prefer to follow the source-target model for it suits my interests - the philosophical assessment of the role of certain theoretical frameworks in scientific progress. This is why I use the word "path".

reductionist trend of finding simple rules for the assembly of big molecules from simpler ones succeeded for some polymers like sugars and fats and biochemists were hoping that the synthesis of other polymers like nucleic acids and proteins would conform to similar assumptions. But that proved to be wrong.

In 1933, Levene proposed the tetranucleotide theory according to which, DNA was a repetitive structure composed of four nucleotides in equal amounts (Morange 1998, p. 34). It was already known that the nucleus of cells contained the genetic material (chromosomes). It was also known that chromosomes consisted of DNA and proteins. But if DNA is just a repetitive polymer like a sugar, it wouldn't be a good candidate for carrying the genetic information needed to specify the complex structure of organisms. A polymer that has similar structure in different organisms can't explain differences. It is not a good difference maker. Thus, DNA was supposed to be the material support of proteins which were thought to do the real genetic job of determining the specific properties of individual organisms.

Erwin Chargaff was the first to challenge the idea that DNA was a simple repetitive structure and the idea that it was composed of identical amounts of each nucleotide. He showed that different species had different amounts of nucleotides in their DNA and that nucleotide amounts were not identical even for individuals of the same species. He showed that there was a different rule (the Chargaff rule) that cytosine ratio equals guanine ratio and adenine ratio equals thymine ratio in DNA (Ibid., p. 38). His findings demonstrated that DNA isn't as simple as first thought to be. However, this still didn't clarify what genetic role DNA played.

Oswald Avery showed for the first time that genes were made up of DNA. He worked with pneumococci, a type of bacteria that had two types of strains. Rough strains, who couldn't synthesize capsule proteins, were non-infectious. Smooth ones with intact capsules were infectious (Ibid., p. 31). The properties of being rough or smooth were believed to be genetic.

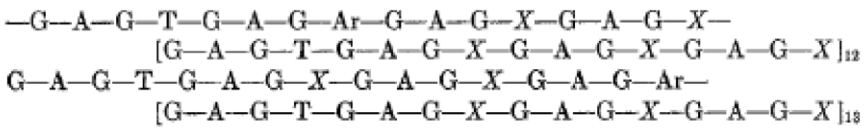
In 1928, Fred Griffith had mixed alive rough bacteria with dead (killed by heat) smooth bacteria and injected the mixture to mouse. He had observed that the mouse was infected. In a sense, some portion of the smooth dead bacteria had transformed rough alive bacteria. Rough bacteria had gained the genetic property of infectiousness.

Avery tried to isolate the component which was responsible for the genetic transformation observed. After isolating it to a good degree of purity, he observed that it didn't denature at temperatures that would denature proteins. Upon colorimetric analysis, he saw it was mostly composed of DNA. He also saw that it wasn't digested by enzymes that cut RNA (i.e. it wasn't RNA) and it was digested by unheated serum, which was known to digest DNA (p. 32). But his finding wasn't well received because the tetranucleotide theory was still popular.

A better received finding that showed the genetic role of DNA came in 1952 by Hershey and Chase. They used bacteriophages (viruses that specifically infected bacteria) and bacteria as model organisms. They first grew bacteriophages with radioactive sulphur and radioactive phosphorus. Radioactive sulphur was integrated into proteins and radioactive phosphorus was integrated into DNA. Then they let the radioactively labelled phages infect another bacterial culture. A few minutes later, they separated the virus from bacteria by using a blender. They saw that radioactive sulphur, which was supposed to be part of phage proteins, was in the solution and radioactive phosphorus, which was believed to be part of phage DNA, precipitated with the bacteria (Judson 1996, p. 109). Since, the infecting or replicating part of phage should enter the bacteria, they recognized that DNA is the genetic material of bacteriophages.

The idea that biological polymers were synthesized by simple rules of repetition was also applied in protein chemistry. For instance, in 1937, Max Bergmann and Carl Niemann proposed the theory that proteins were assembled according to the rule of 2^nX3^m (Bergmann and Niemann 1937, p. 187). According to that rule, the total weight of amino acids is calculated by the formula $\upsilon X2^nX3^m$ where υ is the Svedberg unit

and *n* and *m* are whole numbers (Ibid.). They studied the fibroin protein and proposed that its structure was as follows (p. 188):



As you can see from the picture, fibroin showed a repetitive structure that followed a certain rule. The rule was that the interval between certain amino acids (i.e. glycine, alanine, tyrosine and arginine) was constant. In fact, the structure is fairly correct. Our recent knowledge confirms that fibroin has a region between the 149th and 5206th amino acids in which, it shows a high rate of repetition.[59] But it is a property expected in a protein like silk fibroin which has to be stable. The mistake was with generalizing it to every protein. Bovine insulin, for instance, doesn't have any such repetitive structure.[60]The important point, however, is that even if every protein had repetitive sequences, it would still be true that their sequence isn't determined by some rule of amino acid assembly but by the DNA sequence alone (given that there is no RNA splicing or editing).

Another obstacle against the characterization of the specific structures of proteins was the colloidal theory. Jacques Monod claims that one of molecular biology's conceptual revolutions was the replacement of colloidal theory with the structural or macromolecular theory (Judson 1996, p. 187).

The theory of macromolecules - very big molecules composed of smaller molecules - was not universally accepted until 1930s. The idea of big molecules was out there, since Kekule had proposed the polymer concept in the latter half of 1800s. A polymer is composed of monomers - subunits - with the help of strong chemical bonds. But a polymer need not be a macromolecule. For instance, a polypeptide composed of

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[59] See http://www.uniprot.org/uniprot/P05790 for further information, especially under the title "Sequence Annotation".

[60] See http://www.uniprot.org/uniprot/P01317 for further information.

fifteen amino acids is a polymer, but it is not a macromolecule. A macromolecule is a much bigger molecule and biochemists of early 20th century could not handle, let alone examine them, without breaking them into pieces.

The chemical study of cells had identified many small molecules whose reactions could be explained by the laws of chemistry. Vitamins, amino acids and other such molecules obeyed those laws. Hopkins (1914) proposed that these simple molecules were shown to be central in metabolic processes, as opposed to mere end products like those found in excretion. He believed that these simple molecules, not the complex molecules, were the main targets of research in the biochemical study of metabolism:

> My main thesis will be that in the study of the intermediate processes of metabolism we have to deal not with complex substances which elude ordinary chemical methods, but with the simple substances undergoing comprehensible reactions (Hopkins 1914, p. 653).

Bigger molecules like proteins seemed to conflict with these laws. For instance, Henry's law stated that the concentration of a dissolved gas is directly proportional to its specific pressure just outside the liquid. Blood, however, can carry much more oxygen than Henry's law permits.[61]Another example concerns the viscosity of solutions: some solutions showed a much higher viscosity than expected from the laws of chemistry which say that the viscosity of a solution is a function of the viscosity of the solvent, the size, density, charge of the solute. The colloidal theory explained those deviations by proposing the colloidal state of matter in which "ordinary laws of chemistry - the laws of constant and multiple proportions and the law of mass action - are not applicable." (Olby 1974. p. 7).

The colloidal theory was a bridge or a black box between well studied, simple reactions and complex cellular properties:

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[61] This is because of the intricate structure of hemoglobin, a four subunit protein which weighs nearly 67.000 times a hydrogen atom. In Max Perutz' words hemoglobin was "an organ on a molecular scale" (Judson 1996, p. 188).

> The highly complex substances which form the most obvious part of the material of the living cell are relatively stable. Their special characters, and in particular the colloidal condition in which they exist, determine, of course, many of the most fundamental characteristics of the cell; its definite yet mobile structure, its mechanical qualities, including the contractility of the protoplasm, and those other colloidal characters which the modern physical chemist is studying so closely (Hopkins 1914, p. 662).

The colloidal theory conflicted with the view that proteins have precise structures. Biochemists believed the forces that keep together the atoms in a simple molecule are different from the forces that keep together the constituent molecules in those big molecules - a viewpoint that is directly opposed to the idea of a macromolecule. It was thought that any apparently big molecule (e.g. proteins) in the cell was the product of small molecules coming together in solution and forming amorphous conglomerations. They were thought to be aggregates which are held together by some unknown "aggregative forces" (Olby 1974, p. 9). The chemical composition of proteins was thought to reflect a dynamic equilibrium of different amino acids in the solution (Judson 1996, p. 187). But with the crystallization of urease in 1926, an enzyme, it became clear that proteins were not mere conglomerations of amino acids, they had specific structures.

Since enzymes are proteins and their structures explain their functions, heritable changes in protein structure showed that the main function of genes was to determine protein structure. Beadle (1945) had stated that "the gene's primary and possibly sole function is in directing the final configurations of protein molecules". His methods were not suitable to verify this, and probably, the phrase "directing the final configurations of proteins" was inspired by Linus Pauling's studies on the specificity of antibody-antigen relations (Olby 1974).

Linus Pauling, in 1949, showed that sickle cell anemia was caused by an abnormal hemoglobin molecule (Morange 1998 p. 124). For the first time an inherited disease was shown to involve a change in a molecule. In 1956, Vernon Ingram showed which specific amino acid changes caused the disease. Genes weren't only "directing" protein structure, they were *determining it to the single amino acid level* (Ibid. p.

125).

After the structure of DNA was established and Sanger completed sequencing bovine insulin, the idea that DNA and proteins were repetitive polymers lost its strength. Watson and Crick, in their paper published in May 1953, confidently claimed that "the precise sequence of the bases is the code that carries the genetical information" (Watson and Crick 1953b, p. 965). They assumed that the regularity of the sugar backbone of DNA didn't imply that the pair of nucleotide sequences inside were necessarily regular. In other words, they hypothesized that despite the apparently regular overall structure (i.e. the double helix) DNA could still have an irregular (non-repetitive) structure inside.

After their paper in *Nature*, Watson and Crick received a letter from George Gamow who proposed a theoretical model to explain how DNA sequence determines protein sequence. For the first time Crick and Watson encountered the idea that coding problem can be approached from a theoretical (i.e. not biochemical or genetic) angle. But what is the coding problem anyway?

There are twenty amino acids commonly found in organisms. There are four types of nucleotides in the DNA. We can consider amino acids and nucleotides as letters and the coding problem as the problem to determine which combination of nucleotides corresponds to which amino acid. In a single stranded DNA, nucleotides are connected to each other on a linear string. Amino acids in a polypeptide form a linear string as well. So, it is reasonable to suppose that a single strand of DNA and a polypeptide are colinear. In a schematic form, colinearity looks like this:

CTGCAGAACGGG….

Al-Val-Arg……

If the code consisted of 2 nucleotides per one amino acid, then there had to be only 16 (4^2) words for 20 amino acids in the DNA language, which is inadequate. If it had 4 nucleotides, there would be 256 (4^4) words which leads to redundancy. If the code

consisted of triplets, there would be 64 words. Hence, triplet codons, just on theoretical grounds, seemed to be the best option (Crick 1988, pp. 89-90).

George Gamow, a Russian physicist who had migrated to the US, had suggested that DNA acted literally as a template in protein synthesis (Ibid. p. 91). In other words, he thought proteins were assembled directly on the DNA. According to his scheme, there were diamond shaped holes on DNA where each amino acid fitted. Diamond shaped holes consisted of neighboring nucleotides. The code had overlapping letters because diamond shaped holes shared nucleotides on their borders (Hayes 1998). Gamow also provided a list of 20 amino acids.

Watson and Crick immediately saw some defects in Gamow's code. They first refuted his list of amino acids and constructed their own list of 20 amino acids (Ibid.). They also knew that RNA was involved in protein synthesis. It had already been shown that quickly growing tissues (i.e. root tips, eggs, nurse cells) produced more RNA and it was observed that RNA is located in the cytoplasm whereas DNA is exclusively found in nucleus in higher organisms. These findings suggested that protein synthesis was happening in the cytoplasm where no DNA is found (Judson 1996, p. 243). So, some molecule - probably RNA - was transferring the information on the DNA to the cytoplasm where protein synthesis occurs. Another problem with Gamow's scheme was that the structure of diamond holes in the DNA weren't specific enough to distinguish similar amino acids like valine and leucine.

In 1954, Gamow founded the RNA Tie Club, a club where informal gatherings about the coding problem were organized. In discussion with Crick, Watson and Sydney Brenner, he developed further coding schemes with RNA as template. In his last attempt, he again formulated an overlapping code in which 64 possible triplets were organized into 20 different equivalence groups for each amino acid (Ibid.). But the new scheme put some restrictions on the set of amino acids that can come together in the protein, which proved to be wrong when new protein sequence data became available. For instance, in Gamow's model, neighboring nucleotides restrict which amino acid can be placed besides which amino acid. But his scheme was in

contradiction with the sequence of insulin (Ibid. p. 263). But a more detailed experimental refutation was not given yet in 1953.

The weakest point in Gamow's schemes is that they all were based on overlapping codes. Gamow chose overlapping codes in order to reduce the number of sense triplets from 64 to 20. He also aimed to solve the synchronization problem by overlapping codes since there were no punctuation marks on nucleic acids to show where to begin and where to end protein synthesis. Sydney Brenner, another member of the RNA Tie Club and Francis Crick's later associate, refuted overlapping codes by rigorous statistical reasoning.

In Gamow's overlapping code, 4 repetitive triplets (e.g. GGG) were already considered nonsense. Every triplet can follow or be followed by at most 4 types of triplets: (AXY, UXY, GXY, CXY) – *XYZ* – (YZA, YZU, YZG, YZC). Hence, every amino acid can follow and be followed by at most 4 types of amino acids. But cysteine has been found to follow 14 types of amino acids and to be followed by 15 types of amino acids in proteins. Along with other data, Brenner later demonstrated that there should have been at least 70 types of triplets, which was impossible purely on theoretical grounds: a triplet code with only four nucleotides could only produce 64 triplets (Brenner 1957).

As mentioned before, Gamow's schemes restricted the neighboring relations among amino acids. In other words, not any amino acid could pair up with any amino acid. Brenner wanted to test the idea. He wanted to know whether amino acid pairings were random or *nonrandom*, as supposed by Gamow. He prepared 20x20 cells for each possible amino acid pair. He incremented the number in each cell if actual protein sequences had that pair. If the 20x20 table showed Poisson distribution, it would be good evidence that pairings were random (Judson 1996, p. 285). In other words, it would show that there was no restriction on what amino acid can precede or proceed a certain amino acid in a polypeptide chain. Brenner found that pairings were random and Gamow's last scheme of coding was incorrect.

In 1955, Francis Crick presented an informal paper to the RNA Tie Club. In that paper, he first criticized Gamow's coding scheme and then formulated some excellent ideas such as the adaptor hypothesis and stop codon (p. 292). According to the adaptor hypothesis of Crick, each amino acid binds to a specific adaptor molecule which then carries it to its correct position on the RNA. He thought the adaptor to be a short RNA molecule which has nucleotide complementarity to the template RNA. By this way, amino acids and RNA template were freed from a stereospecificity constraint; the only specificity found here was between the adaptor RNA and template RNA. Stop codon is simply a triplet that signals the end of protein synthesis.

Afterwards, Crick constructed his own coding scheme. It was not only non-overlapping but it also explicitly prohibited overlapping triplets. For instance, in a sequence like AUCGAA, if AUC codes for an amino acid, then UCG or CGA would be nonsense (Judson 1996, p. 317). He also thought that cyclic permutations of sense codes would be nonsense. He also rejected repetitive triplets like UUU. Crick, like Gamow, was trying to derive the number of amino acids (20) from the number of possible nucleotide triplets (64). This was obviously an information theoretic constraint. He wouldn't allow for redundancy in the code. He thought there had to be one to one matching between sense triplets and amino acids.

Things didn't go well for this theoretical scheme either. It was later shown that UUU, a repetitive triplet prohibited by Crick's comma-less code, coded for phenylalanine. Also, on theoretical grounds, it was proved that if cyclic permutations are not allowed, then the complementary strand of DNA would be nonsense and this will reduce codable amino acids to 10.

An experimental finding in 1959 by two Soviet scientists, Belozerskii and Spirin, put the non-redundancy constraint into question (p. 340). Belozerskii and Spirin showed that despite vast diversity of DNA compositions of different types of bacteria, their

protein and RNA compositions were similar.[62] The results suggested that more than one triplet might be coding for an amino acid. Degeneracy, or redundancy, of the code had been rejected by Crick, almost without empirical evidence, just on the grounds that redundancy would reduce the efficiency of information transfer.[63] But in fact, from an evolutionary point of view, degeneracy of the code could be adaptive. In a degenerate code, some nucleotide changes (i.e. point mutations) do not change the respective amino acid and thus, would not result in a loss of function.

The information-theoretical approaches didn't give any successful result. The mathematicians' interest in the problem was at times becoming annoying for experimental biologists. This is obvious from the attitude of Max Perutz, a famous protein crystallographer in Medical Research Council in the United Kingdom. He was receiving letters from mathematicians and information theorists who applied to MRC for cracking the code. Perutz rejected their applications. He said: "We had to write to them that the problem was now not theoretical but biochemical and genetical" (p. 341). Crick summarized their feelings as such: "The whole business of the code was a complete mess, the review for Brookhaven – you can see there, we were completely lost, you see. Didn't know where to turn. Nothing fitted" (p. 342).

In the same period, more biochemically oriented studies of protein synthesis was also being carried out. A part of the puzzle of protein synthesis was to find the intermediates between DNA and the protein. Paul Zamecnik had developed a cell free system to study protein synthesis in 1951 (Morange 1998, p. 133). A cell free (in vitro) system, as the name suggests, is a system that performs a cellular biochemical reaction in a test tube. To construct such systems, one should have a rough idea about the molecular components necessary for the reaction. In 1955, by using a cell free

[62] RNA compositions are similar because most of the stable RNA is found in ribosomes and it is not specific. Ribosomal RNA doesn't code for proteins, it has a structural role.

[63] Gamow's overlapping code was degenerate. Crick in early 1955 had stated, in an informal paper written for the RNA Tie Club, that Gamow's most important contribution to the coding problem was to propose a degenerate, overlapping and absolutely abstract coding scheme (Crick 1955, pp. 5-6).

system, Paul Zamecnik and Matthew Hoagland in MIT began a study on protein synthesis. The 1955 experiment was at first aimed at understanding peptide bond formation. Their cell free system consisted of amino acids, ATP to activate amino acids before peptide bond formation, a fraction of an extract that was supposed to include enzymes and soluble RNA and ribosomes. They put radioactively labeled leucine as a control, to rule out the possibility that labeled ATP is not incorporated into RNA but just clings to it because of sloppy washing. When they saw it bound to RNA, "the control became the experiment" (Judson 1996, p. 313). They continued the control as experiment and in 1956 they found that tRNA-radioactive amino acid complex dissolved and leucine was integrated into the protein. Crick's adaptor hypothesis turned out to be true but he didn't accept it because of size considerations. Adaptor, tRNA, appeared to be much bigger than expected. In any case, the finding was a big step towards the solution of the coding problem. It had identified a crucial component of the protein synthesis machinery - the tRNA.

The beginning of the end for the coding problem came in 1961. Marshall Nirenberg and Heinrich Matthaei reported, in the biochemistry congress in Moscow that they have succeeded in constructing an artificial RNA composed of only uracil, which coded for a protein composed of only phenylalanine. They had used a cell free system similar to Zamecnik and Hoagland's, but they added a synthetically produced poly-U RNA. The artificial synthesis of RNA molecules was enabled by the isolation of the enzyme polynucleotide phosphorylase (Erdmann and Barciszewski 2011, p. 9548). When Nirenberg and Matthaei analyzed the radioactively labeled protein, they found out that it was composed of phenylalanine (Morange 1998, p. 135). They also showed that the code was triplet. Thus, UUU coded for phenylalanine. Using similar techniques, it was discovered that CCC coded for proline.

The in vitro system of RNA and protein synthesis was working for homogenous polynucleotides but the solution of the code required the construction of RNAs with known sequences such as UCA, GCG, etc. Har Gobind Khorana in early 1960s discovered a technique to synthesize RNA with known sequences. In his system,

firstly, short DNAs with known sequences were united by DNA polymerase to build longer DNAs (Khorana 1968). For instance, short DNAs with the sequence CT were linked to form longer DNAs such as ATATATAT... From this DNA, RNAs were produced with the enzyme RNA polymerase. The RNA was then placed into the cell-free system of protein synthesis and the protein's sequence was determined. With the help of these techniques, the code was completely solved in 1966.

The solution to the problem of genetic code came from the biochemistry of protein synthesis and not from abstract theories about information. But from this fact, can we conclude that the concept of information played no role in the discovery? It played a central role, but only when it was given a specific molecular genetic meaning.

Information, as defined by Crick (1958), provides a nontrivial, concise and unificatory account of what a gene is and what it does. In this framework, a gene is a piece of DNA whose ultimate function is to code for a protein and to code for a protein is to determine its amino acid sequence. This idea is nontrivial because there are many other imaginable ways in which a piece of DNA determines the "final configuration of a protein" (Beadle 1945a). For instance, it might have been the case that pieces of DNA acted merely as direct templates that determine the three dimensional shape of a protein, regardless of its amino acid sequence. In this scenario, the coding problem would not emerge, or it would emerge as a completely different problem.

It is concise and unificatory because it assumes a universal and simple relation between genes and proteins. Biochemists were searching for "the code", rather than "a code". Coding rules might have turned out not to be universal and the protein synthesis machinery might have been different in different species. The assumption of universality made it possible to build cell free systems of protein synthesis and let them "read the message" written in the RNA, regardless of the RNA's origin or how it was synthesized.

The formulation of the coding problem relied on the sequence hypothesis. Biochemical study of gene action, in late 1950s and early 1960s, was guided by the sequence hypothesis and the central dogma. These two theoretical assumptions narrowed down the space of possible solutions. Biochemists focused on sequence, rather than other physicochemical properties of DNA, RNA and proteins.[64] The dogma was another guiding principle, which played a negative role "...by suggesting what directions to avoid" (Crick 1988, p. 111). For instance, the dogma prohibited the transfer of information between proteins, and thus, it was never a concern for the biochemists to know the amino acid sequence of the enzymes involved in protein synthesis. So, the concept of information played a positive role in the discovery, despite the fact that abstract considerations about the efficiency of information transfer were mostly useless.[65]

Coding is one founding idea of the molecular biology of the gene. The other is that the action of genes can be regulated.

3.6 The Path to the Bacterial Genetic Regulation

The sequence hypothesis, the central dogma and the genetic code were all ideas about how a certain nucleotide sequence determined an amino acid sequence. They are about the flow of information from nucleic acids to proteins, *given that protein synthesis occurs.* But protein synthesis is a process that has to be regulated, many proteins should be produced where and when needed. For instance, B-galactosidase - the enzyme that digests lactose (milk sugar) into galactose and glucose - should be produced when there is plentiful lactose. Otherwise the cell would be wasting its valuable resources. Genetic regulation ensures this kind of economy in protein

[64] In fact, they attended to those physicochemical properties, such as the activation of single nucleotides, but these were technical problems - they were important for the experiments to work but they did not define the problem for which the answer was sought.

[65] I use the word "mostly" rather than "always" because locking onto a triplet code rather than a quadruplet code was an information theoretic constraint against redundancy.

synthesis. In addition, multicellular organisms have different cell types which share the same genetic material but their protein contents are different. Differentiation of cell types requires that the activities of genes are different in those cell types. Hence, metabolic regulation and the regulation of development depends on differential expression of genes. Genetic regulation is above sequence determination because it goes beyond protein synthesis, it connects different biochemical pathways and it enables the organism to react adaptively to environmental variables (e.g. food, light, heat, signals from other cells etc).

The new viewpoint arising from regulation was cybernetic in spirit. Cybernetic first appeared in military applications such as correcting the trajectories of anti air guns by means of feedback from previous errors (Mindell, Segal and Gerovitch). Problems of cybernetics were at first problems of control engineering. Norbert Wiener, who also worked on such military projects thought that cybernetic ideas like feedback could be applied to biological problems as well. The connection between cybernetics and genetic regulation comes from the fact that just like cybernetic control, genetic regulatory networks react to both internal and external variables in order to maintain a coherent state. Life may be said to necessitate the coupling of different biochemical pathways in a coherent whole. Even a single cell needs such a coherence to continue its life: "And we now know that within each cell a cybernetic network almost as complex, if not more so, guarantees the functional coherence of the intracellular machinery…" (Monod 1972, p. 65).

This regulation is made possible by DNA binding proteins. These proteins recognize certain sites on DNA and their binding either inhibits or facilitates mRNA synthesis, and thus, protein synthesis. Some of these proteins have a peculiar property: the shape of their DNA binding site can be changed by the binding of a regulator molecule to a distant site on the protein. The protein has two shapes - or conformations in the technical jargon - and which shape it takes depends on whether the regulator molecule is attached or not. It also has two binding sites, one for the specific regulator and the other for the specific DNA region it binds. These types of proteins are called

allosteric. The name is a combination of *allo-* which means "other", or "alternative" and *-steric* which denotes "the arrangement of atoms in space", thus allosteric means a molecule that can have alternative shapes. Allostery is not limited to DNA binding proteins, there are allosteric enzymes as well.

Monod, in his *Chance and Necessity*, compared allosteric proteins to transducers in computers (Monod 1972). In a sense, these proteins are small information processing devices. There are three properties of allosteric enzymes or regulatory proteins which make them analogous to transducers:

1) Allosteric proteins have multiple binding sites for different inducers. Thus, they can integrate multiple inputs.
2) Allosteric proteins can be found in two exclusive states (i.e. relaxed and tense). Hence they can produce two outputs depending on the input. That is why he also likens allosteric regulation to Boolean algebra. An allosteric protein is on or off, depending on the presence or absence of the ligand.
3) Ligands (i.e. molecules that bind to the protein) don't have to be stereospecifically similar to the substrate. The allosteric protein has two binding sites, each specific for the ligand and the binding site or the substrate. In a sense, this leads to a symbolic relation between ligands and a form of symbolic computation because this gives the allosteric protein the ability to regulate/catalyze a reaction that is independent of the structure of the regulating substance (i.e. the ligand).

The third property is extremely important because as Crick observed "That meant that you could connect any metabolic circuit with any other metabolic circuit, you see, because there was no necessary relation between what was going on at the catalytic site and the control molecule that was coming in" (Judson 1996, p. 555). If it had been otherwise, as observed in the case of competitive binding of similar ligands to the active site of an enzyme, these proteins would be able to regulate, or be regulated by the same kinds of molecules. Thus, regulation would be confined to the biochemical pathways in which similar chemicals are involved. But the

independence between the active site and the regulatory site in allosteric proteins enables evolution to build "...any physiologically useful controlling connections between any pathways in a cell or in any tissues in an organism" (Monod, Changeux and Jacob 1963, p. 325).

An additional feature of allosteric regulation that makes the analogy of information processing apparently valid is that, ligands don't take part in the reactions catalyzed by the allosteric enzymes (Monod 1972, p. 70). Hence, as in the simple system of an electrical switch and bulb in which the energy is not provided by pressing the switch, the energy of the reaction pathway is not provided from the binding of the ligands or from the ligands themselves.[66]The transfer of information became a distinctive property of organisms opposed to inorganic systems in which the transfer of matter and energy sufficed.

The discovery of the mechanism of bacterial gene regulation - the operon - was made possible by studies on bacteriophage genetics, bacterial mating and metabolism.Max Perutz' and John Kendrew's studies on hemoglobin and myoglobin structure contributed to the development of the idea of allostery.

The first step in bacterial genetics was the acceptance of the idea that bacteria are no more different from multicellular organisms regarding their metabolism. This unifying idea first came with Andre and Marguerite Lwoff's studies on bacterial metabolism. They "showed that all organisms use the same vitamins and coenzymes" (Morange 1998, p. 52). Metabolic pathways were shared by many organisms.

[66] By this I mean the energy is not provided by the binding energies of the bonds in the ligands, since ligands are not metabolized in the process. However, this looks trivial because no complex biochemical pathway derives its energy from an individual step in that pathway. Monod's emphasis on low energetic requirement reflects Crick's idea that the flow of information is a distinctive property of living systems, as opposed to inorganic systems in which flow of energy and matter suffice. Monod is well aware that any kind of computation (information transfer and processing) requires energy, but the source of this energy is not the signal (ligand) itself (Ibid. p. 64).

The other step was to show that variation in bacterial metabolism was caused by mutations and was heritable. In 1941, Beadle and Tatum had demonstrated the existence of mutations which affect metabolism in *Neurospora*. In 1943, Luria and Delbrück showed that bacteria carried mutations which influenced resistance to phage infection. When bacteria were incubated with phage, most died because of infection but some seemed to be resistant. The question of the experiment was to determine whether this was due to a heritable difference or it was due to induction by the phage. In other words, resistance might be brought out by a genetic change or merely a phenotypic change. Luria and Delbrück incubated many cultures with phage for some time and counted the number of resistant bacteria. They predicted that if the phage induces resistance (i.e. the change is only phenotypic), there will be less variation than the case of a heritable mutation. They found that resistance was heritable. Thus, bacteria turned out to be suitable for genetic analysis.

In 1946, Joshua Lederberg and Edward Tatum showed that bacteria could mate. Before that, mutant bacterial strains that couldn't metabolize this or that chemicals were already known. But nobody had observed recombination between these mutant bacteria and bacteria were thought to reproduce exclusively asexually. Lederberg investigated the possibility of bacterial mating by growing two types of bacteria with multiple metabolic deficiencies in the same culture and observing genetic changes. He obtained two mutant *E. coli* strains. One of the mutant strain was deficient in synthesizing methionine and biotin, the other couldn't synthesize proline and threonine (Judson 1996, p. 362). Lederberg and his supervisor Tatum grew them in the same culture and observed that a minor fraction could synthesize all four substances, just like wild type (non-mutant) bacteria would do. They proposed that transfer of genetic material between two strains had happened.

Genetic recombination in bacteria wasn't always happening by direct contact. Sometimes viruses carry parts of their host's DNA to other hosts. This phenomenon was first observed with bacteriophages. For such gene transfer to occur, phage should insert its DNA into the host's DNA. During that period, viruses stay dormant in host's

DNA. However, some external factors can induce the virus to begin reproduction and destroy the host. Upon leaving the host, virus takes part of its DNA. The phenomenon is called lysogeny. The dormant virus is called a prophage. The conversion from prophage to the active virus looked spontaneous. Lwoff, in 1949, showed that prophage could be induced by UV radiation. Two years later, Joshua Lederberg proved that gene transfer in the case of lysogeny didn't require direct contact between bacteria, as it was in the case of mating.

Studies of lysogeny and conjugation not only showed that phages and bacteria were good systems to carry out genetic research but also provided the tools for studying the genetic regulation of bacterial metabolism.

Monod's studies began on the interface between bacterial biochemistry and genetics. Beginning from 1940, he studied a phenomenon called "diauxie" seen in E. coli. When E. coli is grown in a medium containing glucose and lactose, the bacterial population first grew steadily, then entered a state of stasis, then reentered a steady growth period and finally reached a state of stasis. This so-called double growth curve indicated that bacteria were first using glucose and after some delay, they were using lactose. The question was to determine why lactose consumption didn't start at the same time as glucose. Lwoff had proposed that the enzyme that digests lactose (β-galactosidase) was *adapting* to lactose's presence in the meantime (Judson 1996, p. 353).

Enzymatic adaptation was a descendant of Pauling's induced fit model of protein specificity. He thought enzymes acquired specificity for their substrate by molding around the substrate. This kind of induced specificity implied at least part of enzymes were flexible. A related idea about enzyme activation was that the enzymes were produced as inactive precursors and then were converted to the active form by means of induction. Nobody in that period (1940s) thought that the activity of an enzyme could be regulated at the genetic level, i.e. the level of the synthesis of the mRNA for the enzyme.

In 1943, Monod began studying the enzyme adaptation hypothesis with respect to the lactose metabolism in *E. coli*. There were some strains that couldn't metabolize this milk sugar but when they are incubated in the presence of lactose for some time, there appeared some colonies that could utilize lactose. The question was to determine whether a mutation caused this or that the bacteria *adapted* to the presence of lactose, an apparently Lamarckian form of transformation. The results showed that a genetic transformation - mutation - had occurred but the new colonies still showed the double growth curve. Monod interpreted the results as showing both hypotheses were correct: there was a mutation, but after the mutation, the bacteria still had to adapt their enzymes to the presence of lactose.

Lactose is a dimer composed of one molecule of galactose and one molecule of glucose. β-galactosidase cuts it specifically from the β-carbon of galactose. β-galactosidase had already been isolated by means of rabbit antibodies. Hence, it was possible to determine whether bacteria produce it. As of 1949, Monod had better tools to investigate the situation, such as lactose analogs to control the activity of the enzyme without activating the synthesis of the enzyme.

The trick in Monod's studies was to manipulate β-galactosidase activity by lactose analogs that interacted with the enzyme (or the system that regulated it) in different manners. For instance, ortho-nitrophenyl galactoside was composed of galactose and ortho nitrophenol. When it was digested by the enzyme, the ortho nitrophenol part gave a bright yellow color in the culture (Judson 1996, p. 373). This showed β-galactosidase was active. Another analog, which had a sulphur atom near the bond, stimulated enzyme production without being digested. Another one with a methyl group in the place of glucose totally inhibited the enzyme. After these studies, Monod changed the term "adaptive enzymes" with "inducible enzymes" because the phenomenon was no more a case of adaptation - a gain of function directed by the presence of the substrate - it was rather a more general phenomenon of induction - the activation of an enzyme, which was not necessarily useful to the organism (Morange 1998, p. 152).

The next step in induction experiments - in 1951 - was to demonstrate that the enzyme beta-galactosidase was being produced anew – they weren't already there waiting for conversion by an inducer (Judson 1996, p. 377). For this, Monod and Cohn found mutants which couldn't produce tryptophan, phenylalanine or alanine - constituents of the enzyme beta-galactosidase as well as many other proteins. They put the mutants into broths that had very low amounts of these amino acids. The synthesis of the enzyme stopped when those amino acids were depleted. Then they added the inducer. Only trace amounts of β-galactosidase was found in the medium. Finally they added the lacking amino acids. They found much more β-galactosidase. This supported the view that enzyme was being synthesized de novo.

Monod prepared a more complicated experiment to demonstrate that β-galactosidase was being produced anew rather than being converted from an inactive form. In the first phase, he fed the bacteria with radioactive sulphur. It would incorporate into cysteine and methionine. It will be depleted in time. In phase two, non-radioactive sulphur and the inducer was added to the medium. After the sulphur was depleted, β-galactosidase was isolated using antibodies. The result was that β-galactosidase wasn't radioactive but many other proteins were. The experiment showed that β-galactosidase wasn't produced from a precursor and proteins were stable, without much turnover (Judson 1996, p. 380).

While Monod was carrying out his biochemical line of research, François Jacob was conducting genetic research on a peculiar strain of E. coli: Hfr strain of K12 type. Hfr stands for high frequency recombination. The strain was first presented by Hayes, in Cold Spring Harbor Symposium in 1953. Wollman and Jacob, between 1954 and 1955, used this strain to understand the exact timing of gene transfer in conjugation. They interrupted conjugation by using the brute force of a blender. The blender separated male bacteria from the females (hence they call the phenomenon *coitus interruptus*) and only some genes pass to the female. The timing showed the relative positions of genes on the male chromosome (p. 384). Bacterial mating was leading to gene mapping, just as Morgan's studies produced in Drosophila.

In 1955, Cohn and Monod found that a second enzyme, galactoside permease was also necessary for lactose metabolism. This discovery showed that genes that control synthesis were distinct from those which determine the structure of proteins. In some bacteria called constitutive mutants, the protein is synthesized but it is not regulated by the presence of lactose.

In 1957, Jacob-Monod collaboration began. Their independent studies were converging on very similar topics. Monod had been interested in the biochemistry of enzyme induction while Jacob was approaching a similar question from a genetic standpoint. Their collaboration resulted in the famous PaJaMo (short for Pardee-Jacob-Monod) experiments and the discovery of operons.

In 1957, Jacob and Monod designed a conjugation experiment with two types of bacteria. The male (donor) bacteria had intact genes for both the regulatory protein and β-galactosidase whereas the female could produce neither of them. Schematically, male was I^+Z^+ and the female was I^-Z^-. The question, according to Jacob was whether the female would be "both inducible and able to make the enzyme" (Judson 1996, p. 392).

In 1958, Pardee, Jacob and Monod conducted the experiment. After 3 minutes, β-galactosidase synthesis began in the absence of inducer. Approximately two hours after that, synthesis stopped. As a control, they recombined a mutant male (mutant for the inducer gene and β-galactosidase gene) with a wild type female. No synthesis occurred. The results showed that *I* gene was producing a repressor rather than an inducer. In the first case, wild type male's DNA provided the intact gene for β-galactosidase synthesis in the absence of an inducer because there was no repressor in the female. 120 minutes of delay indicated the time needed for the synthesis of repressor from male's intact gene. In the control, the female already had synthesized the repressor so no synthesis occurred.

The results of PaJaMo experiments can be explained by inhibition of a repressor by lactose. I^+ synthesizes a repressor rather than an inducer. Along with the results about

permease and phage induction (i.e. whole set of phage genes should be induced in order for replication), Jacob concluded that there must be a single *switch* that regulates a *battery of genes*. He thought that the repressor acted directly on DNA, not on any downstream element of protein synthesis. He also thought that rate calibration of β-galactosidase synthesis would be achieved by oscillations (on-off) of the gene (Ibid. pp. 402-404).

Regulation by interacting with DNA invoked one important question: Is there a specific place on DNA where the repressor binds? Monod says, given that regulation is at the genetic level, "… there had to be something which received, which was the acceptor, for the repressor that we had to postulate". The site where repressor binds is called the operator. Its location on the bacterial chromosome was discovered using constitutive mutants again. But this time, mutants were producing the repressor without being able to use it. These mutants didn't have intact binding sites for the repressor. Operator, according to Jacob, was like a receiver. Operator constitutive mutants lacked a receiver (Ibid. p. 409). By the same experimental techniques used in previous studies (e.g. coitus interruptus), they located the operator. The sequence was Y-Z-O-I (Ibid. p. 411).[67]Operon, in this model is the set of genes that are regulated by a single operator sequence and the operator itself. Jacob et al. described the operon model in 1960 as such:

> The hypothesis of operator implies that between the classical gene, an independent unit of biochemical function, and the entire chromosome, there exists an intermediate genetic organization. This comprises *coordinated units of expression (operons)* made up of an operator and the group of structural genes coordinated by it (Jacob, Perrin, Sanchez and Monod 2005 [1960], p. 519).

The regulation of enzyme synthesis was only one part of the story of regulation. It was obvious from the functioning of the repressor that it had a specific binding site for the operator - a region on DNA - and lactose which inhibits it. So, the repressor

[67] Y: Permease, Z: β-galactosidase, O: Operator, I: Repressor

had binding sites for two stereospecifically irrelevant molecules and it has at least two conformations one of which is active and the other is inactive.

Proteins that show cooperativity in their behavior were already known before 1960s. Hemoglobin's oxygen binding curve is an excellent example of this. Hemoglobin's affinity for oxygen increases when one or more of its subunits are bound to oxygen (Nelson and Cox, p. 214). Cooperative behavior, along with the finding that deoxy-hemoglobin (hemoglobin without oxygen) and oxy-hemoglobin had slightly different structures were clues for allostery.

In 1959, Jean Pierre Changeux began studying with Monod on "the feedback control of threonine deaminase by isoleucine" (Judson 1996, p. 548). Isoleucine is the end product of a pathway that begins with deamination-dehydration of threonine.[68] It is important to note that threonine is structurally different from isoleucine. Hence, the feedback regulation of threonine deaminase (or dehydratase) by isoleucine cannot happen by means of competitive binding to the active site. This made the phenomenon interesting. Changeux, while studying this, made two important observations: the enzyme had subunits and when heated, it lost its capacity to be regulated by isoleucine while retaining its catalytic power. In 1961, he and Monod proposed that the catalytic and regulatory sites of the enzyme were distinct. Then, Jacob and Monod named the phenomenon as allosteric inhibition. They emphasized the freedom from stereospecific similarity and made the inference that "the enzymes subject to this effect must be considered as pure products of selection for efficient regulatory devices…" (Ibid. p. 550).

In 1962, Monod, Wyman and Changeux proposed their model of allosteric regulation. According to this model, allosteric enzymes had at least two subunits. The binding of the ligand changes the structure of the enzyme and thus its catalytic properties. In

[68] http://www.biocarta.com/pathfiles/isoleucinePathway.asp

addition, ligand interacts with the substrate indirectly by means of the enzyme: binding sites for the two are distinct.

The operon model, along with allostery, was a conceptual breakthrough in genetics. It brought out an enriched concept of the gene and gene action. In the sequence hypothesis, the gene is a static information source. It carries the specifications to create a protein. In the cybernetic model, the genetic material specifies both the structure of proteins and at least some of the *conditions* under which those proteins will be produced. Allosteric proteins act as "regulatory sensors, or master switches" that turn genes on or off, depending on the presence of appropriate signals (Mukherjee 2016). This enriched information concept leads to the idea of a genetic program, a set of genetically coded instructions to build and maintain an organism.[69]

3.7 Conclusion

In the first chapter and the present one, the focus was on what a gene is and what a gene does. In other words, the nature of genes and the mechanism of gene action were at the center stage. In Mendelian genetics, the nature of genes could only be inferred from the gross phenotypic effects of mutations. In molecular genetics, the chemical nature of the genetic material was identified and gene action was conceptualized as coding for a protein plus the capacity to respond to external stimuli by changing the rate and timing of protein synthesis.

Although information related concepts played some role in this development, no a priori mathematical treatment of the concept of information (e.g. considerations about the efficiency of information transfer across generations) appeared to be as important as expected. But information in the sense of structural and causal specificity was a

[69] See Peluffo (2015) for Jacob and Monod's earlier, unpublished views on the "genetic program" metaphor and how these views evolved.

major contributor in every step of progress. Genes are the specific determinants of protein structure and their activity is regulated by specific DNA binding proteins.

These answers only refer to the structure and modus operandi of genes: what they are and how they act in contemporary organisms. But life on earth has an evolutionary history and genes must have played an essential role in the evolutionary process, since they are the bearers of hereditary information. How genes were conceptualized in the theory of evolution is the topic of the next chapter.

CHAPTER 4

GENES IN EVOLUTION

4.1 Introduction

The Mendelian gene explained heritable phenotypic differences in experimental populations. The molecular gene was a source of information to build proteins - the ultimate units of function in the cell. The totality of genes in an organism - genome - carried the genetic program: the information to build a functioning organism. These two perspectives - namely, the Mendelian and molecular perspectives - focus on what genes are and what genes do in the modern organisms. However, there is a history behind modern organisms. Their genomes have been shaped in evolution. The genes, the genomes and the organisms are all evolved structures. Thus, a history of genetics must contain what role the gene concept played in the development of the theory of evolution and how it was shaped by that development.

The theory of evolution is based on two basic ideas. First one is that, all organisms have a common ancestor, from which the diverse array of species have evolved. This is the tree of life hypothesis (Sober 2000, p. 7). The tree of life hypothesis implies that modern species are *modified descendants* of earlier organisms. But how and why were those ancestral species modified? This question brings us to the second idea: natural selection (Ibid).

Natural selection is a process in which organisms better adapted to a certain environment outreproduce their competitors. This changes the distribution of types of organisms in a population. Natural selection leads to a gradual enhancement in organisms. It is a cumulative process. Accumulation of improvements requires inheritance. So, the process must involve genetic differences. The nature of these

genetic differences is of utmost importance for the theory of evolution. Should those differences be small or large? Should they be discrete or continuous?

In the wake of the 20th century, Mendelian genetics and Darwin's theory of evolution came into conflict because they gave different answers to the questions concerning the nature of genetic variation. Darwin's theory placed much emphasis on small, continuous differences and Mendelians worked with large, discrete differences called mutations.

The conflict was not limited to the nature of heritable variation, the efficiency of natural selection was also put under question by Mendelians. Evolutionists, on the other hand, represented Mendelian mutations as anomalies and Mendel's laws as applicable to a very limited set of phenomena.

The resolution of these discrepancies came from the realization, in Mendelians' side, that some principles of Mendelian genetics - discrete differences in characters, complete dominance - could be revised in order to handle the phenomena of continuous variation. The development of the polygenic - i.e. multifactorial - models of inheritance was the key to the reconciliation.

The change in perspective can be traced in Morgan's changing attitude towards the theory of evolution. He was first a follower of De Vries' mutation theory, which stated that a single mutation could produce a new species. Morgan's ideas on the effects of mutations changed in 1910s and this followed a change in his attitude against Darwin's theory.

Around the same period, Ronald A. Fisher was working on the problem of explaining continuous variation on the basis of Mendelian principles. Biometry - the mathematical study of the inheritance of continuously varying traits - was a field that had developed independent of Mendelian genetics and there were serious disagreements between the two schools. In 1918, Fisher published a paper in which he derived the generalizations of biometry from a Mendelian population genetic model. This was a milestone in the emergence of the Modern Synthesis.

Modern Synthesis - or Evolutionary Synthesis - is an updated version of Darwin's theory of evolution. The "update" came through the developments in population genetics, systematics, experimental genetics, and paleontology.

Population genetics contributed to the synthesis by making evolution tractable through mathematical models. These models depended on simplifying assumptions which had an impact on how genes were conceptualized. The internal structure of genes and physiological mechanisms of gene action were ignored for the sake of capturing population level dynamics of evolution. This led to the famous "bean bag genetics" dispute. According to Mayr (1959), population genetic models were oversimplifications that could not capture the intricacies of the evolutionary process in the wild. Mayr heralded that a new theory of evolutionary genetics - the genetical theory of relativity - was in the making.

Considering the works of the founders of population genetics, Mayr's criticism was unfair because they, most prominently Wright, had attended to the effects of gene-gene interactions and other complications. Still, Mayr had captured an important deficit in the conceptualization of evolution in these models. Individual genes - more correctly, their alleles - were taken to be the units of evolution. The process of evolution was depicted as if it was a matter of allele substitutions, regardless of the causal structure at which evolution proceeded. This causal structure was an interactive one and even if Mayr's "genetical theory of relativity" has not been built yet, his insight that there is more to evolution than allele substitutions is still correct. But an opposing view was developed by an influential evolutionary biologist George C. Williams and it was elucidated and popularized by another biologist Richard Dawkins. The opposing view - gene selectionism - suggested that individual genes were the units of evolution, and given that natural selection is the most prevalent factor in evolution, genes were the *ultimate* units of selection. This concept of genes - the genes as the units of selection - provides a new dimension to the gene concept. A gene does not only act as a determiner of phenotypic differences - at the level of

observable traits or protein sequences - but it is the ultimate unit at which natural selection leaves its marks.

4.2 Mendelian Genetics and Darwin's Theory of Evolution

Mendelian genetics in its original form seemed to contradict Darwin's theory of evolution or, symmetrically, Darwin's theory of evolution by natural selection seemed to contradict Mendel's laws. Darwin's theory was based on the assumption that the raw material of evolution, i.e. heritable variation, was of a continuous sort.

Height is one such continuously varying trait such that there are almost any intermediate values between two given values. Beak size in birds, leg length in horses, milk yield in cows and sheep are other examples of continuously varying traits. Almost every biologically and economically important trait in the organic world vary continuously.

On the other hand, Mendelian factors are discrete, both in their transmission and in their effects on the phenotype. All of the seven characters Mendel examined came in pairs with no intermediates. Most of the mutations studied by later Mendelians were also discrete. For instance, eye color mutants in Drosophila - e.g. *white, eosin, purple, etc.* - did not form a continuous series, ranging from red (the wild type) to white.

The hypothesis of gametic purity, a central premise of Mendelism, states that factors are transmitted intact and independently into the gametes without blending. Blending would provide a straightforward mechanism that produced intermediate grades of a trait, like every shade of color can be produced by mixing different dies. Blending was prohibited by the principle of gametic purity, the essential principle of Mendelian genetics.

Complete dominance also contradicted with the occurrence of intermediate phenotypes (e.g. the offspring of tall and short parents might have medium height).

The offspring phenotype was similar to one of it's parents, rather being an intermediate between them.[70]

In Darwin's theory of evolution, the main mechanism of evolutionary change is natural selection and the main type of variation which natural selection acts on is continuous variation. For natural selection to occur, there must be heritable variation in fitness in a population. Variation denotes differences in the traits of individuals belonging to the same species. Height differences, differences in the ability to metabolize certain nutrients, differences in behavior, all count as variation. These differences must be heritable - they must be passed onto successive generations in order to be significant in evolution because Darwinian evolution requires accumulation of *beneficial* - i.e. fitness enhancing - variation, in the direction determined by selection. For a difference to be subject to selection, it should have a positive or negative effect on fitness. Fitness is the ability to survive and reproduce. Thus, heritable variation in fitness amounts to the differences of organisms with respect to their viability and producing offspring, which is caused by their heritable trait differences.

If there is "heritable variation in fitness", as defined above, the bearers of beneficial trait variants - e.g. shorter individuals, individuals which can metabolize fats with a higher efficiency, etc. - would outreproduce others and the distribution of traits in the next generation would change in favor of them. If this process is iterated for a number of generations, the population would solely consist of the bearers of that beneficial trait. Darwin (1861) summarized how natural selection worked as such:

> Owing to this struggle for life, any variation, however slight and from whatever cause proceeding, if it be in any degree profitable to an individual of any species, in its infinitely complex relations to other organic beings and to external nature, will tend to the preservation of that individual, and will generally be inherited by its offspring. The offspring, also, will thus have a better chance of surviving, for, of the many individuals of any species which are periodically born, but a small number can survive. I have called this

[70] This doesn't mean that Mendelians never observed such cases in their hybridization experiments.

> principle, by which each slight variation, if useful, is preserved, by the term of Natural Selection, in order to mark its relation to man's power of selection. (p. 61)

For Darwin, slight differences between individuals is the most important source of variation. In the case of animal and plant domestication, humans have selected slight visible differences for generations, so as to produce individuals much different from their ancestors. Natural selection, for Darwin (1861), does the same thing in a much longer time. In *The Origin of Species*, he wrote:

> No one supposes that all the individuals of the same species are cast in the very same mould. These individual differences are highly important for us, as they afford materials for natural selection to accumulate, in the same manner as man can accumulate in any given direction individual differences in his domesticated productions (Darwin 1861, p. 47).

Darwin believed that evolution by natural selection could only work with this kind of variation, because, natural selection is a *gradual* process where the accumulation of small modifications is the *sole driver of evolutionary change*. Darwin explicitly rejected the view that saltations were of any importance in the process of evolution:

> Natural selection can act only by preservation and accumulation of infinitesimally small inherited modifications, each profitable to the preserved being; and as modern geology has almost banished such views as the excavation of a great valley by a single diluvial wave, so will natural selection, if it be a true principle, banish the belief of continued creation of new organic beings, or of any *great and sudden modification in their structure* [emphasis added]. (Ibid. p. 90).

Darwin believed that natural selection could "see" any heritable difference, so long as it had an effect on the survival and reproduction of its bearers. Natural selection produces adaptations by preserving beneficial differences, even if their effects are very small:

> It may be said that natural selection is daily and hourly scrutinizing, throughout the world, every variation, even the slightest; rejecting that which is bad, preserving and adding up all that is good; silently and insensibly working, and wherever opportunity offers, at the improvement of each organic being in relation to its organic and inorganic conditions of life. (Ibid. p. 81).

Not every evolutionist was in the same opinion with Darwin. There were obvious discontinuities in phenotypic trait distributions. Vertebrates and invertebrates differed from each other in many characters and the differences were discontinuous. Intermediate forms between fossils were frequently absent. Discontinuity was an essential part of biological diversity.[71] And this required an explanation in the Darwinian framework. Darwin's explanation was that these discrete differences resulted from a lengthy, cumulative process of natural selection acting on small differences, for long periods of time. This hypothetical explanation did not satisfy many biologists, such as Francis Galton and Hugo De Vries.

Francis Galton, the cousin of Charles Darwin and the founder of biometry - the statistical study of continuously varying heritable traits - was dubious about the power of natural selection in creating adaptive novelty (Bulmer 2003). Adaptive novelty is the evolutionary emergence of new, complex and functional traits such as the eye. He thought that the occurrence of sports - gross heritable changes - was an essential complement to Darwin's theory of evolution. Hugo De Vries suggested gross mutations as a mechanism of evolution that was alternative to natural selection. Hugo De Vries' mutation theory had a serious impact on the thoughts of early Mendelians, concerning their outlook on evolution and mutations. Its impact faded away with the growing knowledge about the nature and effect size of mutations.

4.2.1 De Vries and the Mutation Theory

Hugo De Vries believed that evolution occurred through discrete and observable steps. In the preface of his *The Mutation Theory* he wrote:

> The object of the present book is to show that species arise by saltation and the individual saltations are occurrences which can be observed just like any other physiological process…. In this way, we may hope to realize the

[71] Here, I use the term diversity in the sense of the differences between species, genera or higher taxa. Variation refers to intraspecific, interindividual differences.

> possibility of elucidating, by experiment, the laws to which the origin of new species conform (De Vries 1909, cited in Allen 1969, p. 60).

In this passage, de Vries not only claims that speciation events are saltations rather than gradual changes, but he also says that those saltations are both observable and open to experimental study. This was an important reason why Thomas Hunt Morgan was influenced by De Vries.

What are the mutations of De Vries' mutation theory? According to Allen, "De Vries distinguished three types of mutations: progressive, retrogressive and degressive." (Ibid. p. 61). Progressive mutations were the ones which created new characters *de novo*. These mutations were the most important ones in evolution because speciation events depended on this type of mutation. Retrogressive mutations were losses of certain characters such as the white eye mutation in Drosophila or the loss of variegation in leaves of certain plants. Degressive mutations were heritable changes which made a latent mutation become visible in the phenotype. De Vries believed that retrogressive and degressive mutations followed Mendel's laws but progressive mutations did not. Even if they were unpredictable, it was still possible to detect certain mutative periods in which the organism is more prone to produce offspring with progressive mutations.

De Vries saw progressive mutations as the ultimate source of genuine novelty. He also thought that genuine novelty could not be brought about by a cumulative process. Emergence of novelty was unpredictable. Hybridization of different forms was only a reshuffling of existing variation; no genuine novelty could follow from this mechanism either.

De Vries proposed his mutation theory as an alternative to the Darwinian view that new species emerge by selection acting on "individual variation".[72] Individual variation (i.e. continuous variation) consists of the small differences observed in the members of a species. De Vries believed that selection acting on this type of variation

[72] I have called this type of variation "individual differences" above.

can neither transgress interspecific borders nor create “new and constant characters”. These two objections depended on the idea that individual variation was not heritable (Ibid. p. 72).

Selection, in this context, was seen as a merely negative force which eliminated the unfit. Mutation produced variation, some of which involved great phenotypical changes, and natural selection sorted out unviable variants. It could not produce novel, adaptive characters. Evolutionary novelty came from mutations (mostly progressive ones) for de Vries (Ibid. p. 73).

Why was the mutation theory received favorably? Because it surpassed some difficulties Darwin's theory encountered. One problem Darwin’s theory encountered was the “swamping” problem. Blending inheritance proposed by Darwin led to halving of variation in every generation. This would lead to the elimination of all variation - the raw material of selection. De Vries’ mutations did not blend and this would preserve the variation.

Mutation theory also solved the problem with nonadaptive intermediate steps in the process of adaptation. When an organism enters a mutating period, it throws off sports with totally new traits, without any gradual steps.

Another problem with Darwin's theory was with the timescales involved. Lord Kelvin had calculated the age of the Earth and found that the time was not enough for selection acting on small variations to produce the diversity of life. He estimated that the Earth was between 20 to 100 million years old. Darwin’s mechanism of gradual accumulation was too slow to produce all living forms in such a relatively short period of time. But mutation theory provided a much faster mechanism for the emergence of new species. In addition, mutation theory provided new *experimental data* on the questions concerning evolution. De Vries' botanical garden in Amsterdam astonished experimentalists. He compared the experimental aspect of his work with earlier evolutionists as such:

> The origin of species has so far been the object of comparative study only. It is generally believed that this highly important phenomenon does not lend itself to direct observation, and much less, to experimental investigation… The object of the present book is to show that species arise by saltations and that the individual saltations are occurrences that can be observed like any other physiological process… In this way we may hope to realize the possibility of elucidating, by experiment, the laws to which the origin of new species conform (de Vries 1910, cited by Allen 1969, pp. 83-84).

De Vires claimed to have shown how new species emerged under the controlled conditions of a garden. His lab organism was *Oenothera Lamarckiana*[73]- evening primrose, which continuously produced new "elementary species" (De Vries 1905, p. 521). De Vries' views on species differed from the systematists' tradition of his time. Systematists had classified organisms by means of their phenotypical similarities, but De Vries believed that those "species" were aggregates of many different elementary species, which revealed themselves in hybridization experiments or through unpredictable mutating periods. When he said that *O. Lamarckiana* continuously produced new species, he referred to these elementary species, not the species of systematists.[74]

O. Lamarckiana is an ornamental plant with large, bright yellow flowers (Ibid. p. 524). As opposed to Mendel's *Pisum sativum*, self-fertilization is a rare phenomenon in this plant. Self fertilization reduces the genetic variability, thus, it is reasonable to assume that *O. Lamarckiana* should bear great genetic variation. According to De Vries, the most peculiar character of this plant is that it produces a number of new species each year (Ibid). What are the differences between the original stock, and the offspring, which made De Vries believe that they are new species?

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[73] In modern nomenclature of species, the first letter of the first term (genera) is capitalized but the first letter of the second term (species) is not. But De Vries capitalizes both, so I used his original style.

[74] It is notable that Mendel, in 1865, expresses similar doubts about the reality of systematists' species (p. 44). This might be a general tendency among plant hybridization researchers.

One new type of offspring, which De Vries named *laevifolia*, differed from the ancestors most dramatically with respect to the shape of its leaves. It had smooth leaves, lacking the convexities of the ancestral plants. A less prominent difference concerned the shape and color of flowers.

Brevistylis, another type of offspring, was different from *Lamarckiana* for it had very short styles in its flowers. There were many other phenotypic differences (e.g. leaf shape) as well but the most important fact concerning this type was that when it is self fertilized, it produced pure *brevistylis*, and no reversion to the ancestral *Lamarckiana* type was observed (Ibid. p. 530). In Mendelian terminology, the mutation, which affected many characters, produced a constant genetic change.

These two new types could only be seen as new varieties of the same species. O. gigas and O. rubrinervis were truly new species, according to De Vries because they showed striking differences from Lamarckiana in many respects, such as stem width, fruit shape, coloring and shape of leaves, etc.[75] Their reproductive cycles - biennial or annual - were markedly different from their ancestor (Ibid. p. 536). They also retained the capacity to throw out new types, as Lamarckiana did. De Vries describes this phenomenon such that ".... the instability seems to be a constant quality, although the words themselves are at first slightly contradictory. I mean to convey the conception that the degree of instability remains unchanged during successive generations" (Ibid. p. 545).

De Vries interpreted the results of such experiments as refuting Darwin's theory of evolution and especially his mechanism of natural selection changing a species gradually. The emergence of new species was sudden, without any gradual transformation from the ancestral type to the new types:

[75] De Vries was right in defining these as new species. *O. giga* was a species which emerged by polyploidy, a process which changed the chromosome numbers from 2n (n is the number of the pair of homologous chromosomes, which is 23 in humans) to 3n (triploid) or 4n (tetraploid). *O. giga* was later shown to be a tetraploid (Nei and Nozawa 2011).

> Intermediates between them and the general type were not found, and no indication of their appearance was noted in their parents. They came into existence at once, fully equipped, without preparation or intermediate steps. No series of generations, no selection, no struggle for existence was needed. It was a sudden leap into another type, a sport in the best acceptation of the word (Ibid. pp. 549-550).

The mysterious hereditary behavior of *Oenothera* was later explained as a case of constant heterozygosis. Historically, De Vries' mutation theory was very influential on early Mendelians. It was De Vries' call to an experimental study of evolution and his claim to have produced new species in an experimental population which influenced Thomas Hunt Morgan deeply. Morgan, who was dissatisfied with Darwin's theory of evolution in many respects, began his Drosophila work in order to show that De Vries style mutations also occurred in this organism (Kohler 1994). But Morgan's ideas on mutation and natural selection changed dramatically after many years of experimental work in genetics.

4.2.2 T. H. Morgan: Mutation and Natural Selection

Mendelians at the beginning of 20th century thought that Mendelian theory provided an alternative to Darwinian evolution.[76] They thought, albeit for a short period, that mutation was the key mechanism of evolution and natural selection was impotent in creating new characters and explaining the origin of diversity. T. H. Morgan's evolving ideas on natural selection provide a good view of how Mendelians conceptualized the relation between mutations, continuous variation and selection.

Morgan had many doubts about Darwin's theory. The weakest point in Darwin's theory was the lack of a hereditary mechanism that was amenable to experimental study. Another general problem was that the adherents of Darwin's theory were

[76]William Bateson's *Materials for the Study of Variation: Treated with Especial Regard to Discontinuity in the Origin of Species* (1894) gives a catalogue of 886 cases where discontinuity rules (Schwartz 2008). Bateson, who became the most influential Mendelian in UK after 1900, continued his "especial regard to discontinuity" till his death (Ibid.).

making gross speculations without much empirical support. The third weakness was that Darwin himself, even not willingly, used Lamarckian mechanisms when he had to explain the origin of novel adaptive traits.

Morgan's (1903) first wave of criticism against Darwin began when he realized that the capacity to regenerate lost organs can't be explained by natural selection acting on continuous variation. This is because the gradual steps, before the full-scale regeneration capacity emerges, were useless. In the case of regeneration, an incomplete regeneration - an intermediate form between no regeneration and full regeneration - would not increase the fitness of its bearer. Thus, it would not be selected. The same is true for almost any complex adaptation.

Morgan believed that continuous variation was not the type of variation needed to explain species formation. Selection of continuous variation can change a population within species boundaries, never more. And it was dubious, in early 1900s, whether continuous variation (e.g. variation of height in humans) is heritable (Allen 1968, p. 118).

Selection acting on discontinuous variation was also inadequate in explaining the origin of new species because, the new characters would soon be "diluted" by mating with normals and they would disappear. This was a repetition of Jenkin's swamping argument. According to Jenkin, a sport (mutant) would lose its beneficial character by successive matings with the common type (Bulmer 2003). Suppose that a sport can reproduce two times faster than the common type. Since it is the only one of its kind, it would have to mate with the common type and its offspring would reproduce only 1.5 times faster than the common type. If this sport/common type matings continue, the reproduction rate would soon approach the common type. Morgan believed that only if the mutant type and the common type cannot mate, we can talk about speciation by discontinuous variation. Morgan, like De Vries, assumed that *only* if the ancestral species produce sports with *enough frequency*, the new types can gain a foothold in the population and constitute a new species.

Morgan, like De Vries, considered natural selection as a negative force which only eliminates the unfit but can't produce the fit. Selection can only fix the population in the limits given by the heritable variation already possessed by a population. It can't produce new traits, or change already existing factors of heredity. As mentioned before, Darwin's insistence upon gradual modification by selection did not satisfy Morgan, because intermediate steps would be useless. Selection alone could not explain the emergence of complex adaptations.

Darwinians, who seem to agree with the objection about intermediate steps, invoked Lamarckian principles and Morgan, as an embryologist as well as geneticist, couldn't see how acquired somatic changes could affect hereditary properties. Morgan saw Lamarckian explanations as fancy hypotheses with no experimental support.

Evolutionists invented teleological theories like orthogenesis, internal driving forces guiding the evolutionary trajectory of lineages. Morgan was an opponent of teleology in his understanding of science. Since he saw no escape route from teleology in the theory of natural selection for the reasons above, he rejected the theory itself.

Morgan disliked wild speculations of evolutionists such as Weismann and Spencer. He was an experimentalist and believed that experimental confirmation and disconfirmation is the hallmark of science. Most of the evolutionists of his day could only make field observations, make collections of organisms or gather fossils. Many conflicting theories were proposed to explain this data. Experimental work was lacking (this is why Morgan was so impressed with de Vries' experimental approach). Grand theories were distasteful for Morgan. He liked simpler hypotheses with perfect empirical support. He also liked hypotheses which directed research (he calls them working hypotheses) rather than big theories tailored fit for the data at hand (Allen 1968, p. 123).

Around 1910-11, Morgan was converted into a Mendelian. In this period, Morgan couldn't see a way to reconcile Mendel's theory with Darwin's theory. He thought that Mendel discovered the laws of transmission of characters, not the nature of variation

- the raw material of evolution. He realized that Mendelian mutations were different from both Darwin's "slight individual differences" and De Vries' species creating progressive mutations: "Mendelian variations were too definite (too discontinuous) to be the type of which Darwin referred, and too slight to be the mutations which De Vries emphasized (species creating saltations)" (Ibid. p. 126).

According to Allen (1968), Morgan gradually changed his attitude against Darwinism in the period between 1908 and 1916. As said before, he was hoping to study De Vries type mutations in Drosophila. But the more mutations Morgan encountered, the more he became convinced that the changes accompanying mutations were different from those encountered by De Vries. The changes were less dramatic, they obeyed Mendel's laws.

Fluctuating variation, or individual variation, was seen to be both uninheritable and too small to explain speciation[77]. But Morgan, in his Drosophila work (1909), saw that Mendelian mutations produced individual variation that was heritable and was definite. The accumulation of these heritable and definite variations can transcend species boundaries (*Ibid.* p. 129). So, he gradually distanced himself from De Vries' mutation theory and approached Darwinism, but he kept his reservations for the latter.

In 1910 and 1912, Bradley Davis showed that Oenothera variants were not new species. The original stock was probably a hybrid which dissolved into two "types". Thus, the only observed example of "speciation by a single mutation" collapsed. Morgan's mutations were different in the extent of their effects. They were always in the species boundaries. They could be as definite as white eye or as scute bristles (p. 131). The accumulation of Mendelian mutations in a certain direction could drive the

[77] See Johannsen (1911).

speciation process.[78]Recombination of multiple genes could produce many kinds of variation including continuous variation.

Mendel's classical paper only included discrete and dichotomous characters. But variation in nature was mostly continuous. The first factors discovered in Morgan's lab were also discrete like the white eye, eosin eye, etc. According to Allen, Morgan's group discovered gene interactions (i.e. multiple genes affecting the same property) by 1914-1915. This was important because gene interactions could give the key to reconciling Mendelian genetics with the theory of evolution. The idea of a chief factor and modifying factors, one working in an all or nothing fashion and the others as dosage determiners, gave Mendelians the power to explain continuous variation. Selection acting on modifiers could fix the phenotypic expression of a chief gene by fixing the combination of modifiers or there can be variation regarding the modifiers (p. 134).

Morgan, in most of his career, carried on defending the mutation theory. But his theory differed considerably from the original theory by De Vries. Morgan was well aware that De Vries' original formulation of mutation theory was much more radical than Mendelism. There, mutation was seen as the major driving force in speciation. But in Mendelism of early 1900s, mutation was a change that had local effects (e.g. a specific organ, tissue, etc.). De Vries' mutation theory and the unit character interpretation of Mendelism occupied two extreme positions concerning the width and the depth of effects of single mutations. De Vries' thought a mutation had dramatic effects on multiple characters, such that it could produce a new species with a single stroke. Unit character theorists believed that a mutation had local effects - they influenced only one character, or an aspect of a character. Morgan, on the other hand, believed that the effects of mutations were not confined to a single character. Morgan defended a subtle holism in which every gene affects every character to some

[78]It seems that this idea was first expressed by Hermann J. Muller in 1914. Morgan came to realize its significance in 1916 (in *A Critique of the Theory of Evolution*).

degree but for some mutations and some phenotypical properties, effects are too small to be detected.[79]

These modifications in the conceptualization of mutations made it possible for Morgan to reconcile his type of mutation theory with Darwin's theory of evolution. As of 1916, Morgan could agree with Darwin on the nature of variations. However, Morgan continued to express his reservations about the power of natural selection in creating the diversity and adaptedness observed in nature.

In his *A Critique of the Theory of Evolution,* Morgan referred to some artificial selection experiments in order to show that the effect of natural selection was limited: Artificial selection could change the mean value of a population variable (e.g. average height) but the process came to a halt after a few steps (p. 153) Population mean could not be pushed beyond certain limits. For instance, by selection alone, one cannot obtain watermelons weighing 2 tons or cows giving a hundred liters of milk. There were constraints on the effectiveness of selection and the most powerful of them was the reservoir of genetic variation contained in the population.

For Morgan, another problem concerning the role of natural selection in evolution was that selection could not be the origin of new adaptive traits. Morgan (1916) cites Johannsen's studies on beans to defend this view. According to Morgan, these studies in artificial selection showed that "Selection, then has not produced anything new, but only more of certain kinds of individuals" (p. 154). For Morgan, evolution was more than changing the relative frequencies of already existing kinds in a population. It also consisted of the creation of new kinds.

Most of the followers of Darwin thought that the directed change in a continuously varying trait brought out by selection (i.e. sliding average model as Morgan calls it) could transgress the boundaries of already existing variation in a population. Let's

[79]Subtle holism is also reconcilable with subtle reductionism. I will call this viewpoint the spectrum viewpoint of differential specificity.

consider height. If, upon selection, the tallest individuals in the selected line are taller than the tallest ones in the original population, one can say that selection has produced something more than what was already there in the population. According to Morgan, this is not the case. The experiments conducted by Johannsen showed that selection could not produce *new types*. New types here means genetically homogenous populations whose average values for a certain trait differ from the original mean sizes, and that the difference is heritable. But in the original evolutionary setting, novelty is even more radical than this. Evolutionary novelty means the creation of new functional traits, not just more of the same - gradual rise or decrease in the mean value of a character. Morgan says that Darwin himself recoursed to the inheritance of acquired characters (i.e. the principle of use and disuse) to explain the origin of new functional characters because he knew the difficulties in explaining them by natural selection alone. But inheritance of acquired characters, or any environmentally directed heritable change, was at best a very dubious assumption for Morgan.

Inheritance of acquired characters conflicted with much of the Mendelian experimental work. In Mendelian genetics, factors are not transformed when they are exposed to different environments[80], different genetic backgrounds or somatic settings. For instance, the factors for red and white in the flower four o'clock give pink when they are combined. But backcrossing to the homozygous white or red will produce pure whites and pure reds. The pinkness of their ancestors - a somatic property - has no effect on the factors themselves (Morgan 1926).

Environmentally induced variation was not heritable: In Drosophila cultures, when the culture was moisty and acidic, the abdomen color patterns deviated from the normal pattern. In time, the culture dried and late-hatching flies had normal abdomens. When abnormal flies were transferred to dry cultures, they produced normal offspring. When normal flies were transferred to acidic and moisty cultures,

[80]Here I refer to non-mutagenic environments.

they produce abnormal progeny. Thus, the environmentally induced change was not heritable.

Another reason why Morgan refuted the inheritance of acquired characters was that experimental studies in favor of this hypothesis were very weak. Morgan criticized an experiment on butterfly pupae pigmentation. When these pupae were raised in daylight they were dark but they were greenish yellow when they were raised in a yellow or red surrounding. Dürken raised some pupae in orange light. Then, he collected the eggs and divided them into three groups: first group is raised in orange light, the second in bright light and the third in darkness. Greenish colored pupae are collected from all groups and raised again under orange, bright light and darkness. The interesting result was that, when the greenish pupae coming from the orange lighted population was raised in bright light, there were more greenish individuals than the former population raised in bright light. One might interpret this result as the enforcing effect of environment on a genetic property. But Morgan claimed that the selected pupae were already more sensitive to orange light. He meant that the pupae population which gave higher greenish results already consisted of more numerous light-sensitive individuals. Thus, *sensitivity to environmental variables was itself a genetic property*. The starting population was not genetically homogenous. The environmentally induced change was not inherited, but the capacity to respond to environment was selected, just as any other heritable character is selected. For Morgan, the fault in this study could be generalized to almost every Lamarckian study: "The same error runs through nearly all the work of this sort that has been done. Modern genetics, if it had accomplished nothing more, would have justified itself in showing the worthlessness of such evidence" (Ibid. p. 306).

If Johannsen's experiments have shown that the original population consisted of different genetic types, the role of selection was just sorting them out and inheritance of acquired characters was a desperate hypothesis, how would Morgan answer these questions: What was the origin of novelty in evolution? What role did natural selection play in evolution? For the first question, Morgan mentioned two types of

events. Recombination of genes could produce new traits by means of interaction. *De novo* mutations provided the second source of novelty.

For the question concerning the role of selection, Morgan provided two answers. One is an extension of the point raised above. Sometimes, artificial selection in domesticated animals and plants apparently produces new types. For instance, domesticated plant types are dramatically different from their wild ancestors. According to Morgan, this might be due to the selection of many modifier genes. This was clearly in line with the idea that selection acts on existing variation, since the original population must have been heterogeneous for those modifiers.

The second answer Morgan gave is more a matter of theory than empirical evidence. The suggestion was that, selection "guides" evolution by increasing the probability of the accumulation of mutations in a certain direction. This does not mean that selection guides mutations. It means that, since selection preserves beneficial mutations, it would raise the probability of further mutations *adding up in a certain direction*. His original example is that of the chance of getting 100 heads in a series of coin tossing. The chance depends on both the heads already obtained and the number of future tosses (Ibid. p. 190). The creativity of natural selection is nothing more than this. Morgan criticized those who believed that selection raises the probability of the *occurrence* of future mutations (Ibid. p. 193). Rather, selection raised the probability of the *accumulation* of certain mutations. The former would attribute teleological powers to selection but the second would be more in line with Morgan's reductionist outlook.

The growing body of knowledge about mutations, the rates of their occurrence, their physiological effects, cleared the way for a reconciliation between Darwin's theory of evolution and Mendelian genetics. An important step in the direction of reconciliation was the reduction of biometry to Mendelism, which at least demonstrated the theoretical possibility of explaining continuous variation - and evolution - in the Mendelian framework.

4.3 Biometry, Mendelism and the First Phase of Evolutionary Synthesis

The first phase of Evolutionary Synthesis (1918-1932) refers to the works of Ronald Fisher, Sewall Wright and J. B. S. Haldane (Sarkar 2004). In this phase, the first mathematical population genetic models of evolution were constructed. Many seemingly intractable questions, such as the mutation rate, the power of natural selection, epistasis, etc. were transformed into quantitative problems which could be analyzed with mathematical techniques.

Quantitative study of evolutionary phenomena began with the biometrical school. Biometry and Mendelism were offering contrary positions about evolution. An important contribution of the first phase was the "absorption of biometry into Mendelism" (Ibid. p. 127). It was important because the discrepancies between the two fields created false dichotomies like the ones we saw in the previous section: mutationism vs. selectionism, continuity vs. discontinuity. These dichotomies prevented Mendelians from seeing the importance of the population level regularities and they prevented biometricians from understanding the importance of mutations as the ultimate source of evolutionarily significant variation.

4.3.1 Biometry and Mendelism

Biometry is the statistical study of continuously varying traits. The field of biometry was founded by Francis Galton. Francis Galton was interested in the problems of heredity mainly because of his eugenic ambitions. He developed some of the concepts (e.g. correlation) and methods (e.g. regression) statistics still uses today.

Galton's statistical techniques were developed further by Karl Pearson, a talented mathematician. These techniques and concepts were applied to a number of biological questions by the biologist W. F. R. Weldon. These followers of Galton are more important in our discussion about the relation of biometry to Mendelism than Galton himself because they were the people who guided the empirical and methodological opposition of the school of biometry against Mendelism.

Weldon's most important contribution to biometry was to show the effects of natural selection in a population of crabs in Naples (Bulmer 2003). In that study, he tested for the effects of natural selection on the normal distribution of crab frontal breadth. Galton had proposed that continuously varying characters show normal distribution, according to Gauss' law of errors. He had thought that normal distribution, along with regression to the mean, were universal empirical laws in biology. He also thought that regression was a real force, not a statistical artefact. He even believed that regression to the mean of a population would counter natural selection and make it impotent in making any permanent changes in a population. Weldon's data on crabs showed that natural selection could shift the mean of a population.

When Pearson analyzed the data, he realized that this population consisted of two races with different means and different population sizes. Weldon thought that this could be explained by ongoing natural selection. In his next study, he tried to show that, in a similar mixed population in Southern Plymouth, the two races had different mortality rates. In 1898, Weldon discovered that in the shore crab population in Southern Plymouth, an ecological factor was responsible for the differential mortality rates of different types. In 1893, a breakwater had been built there and silt began accumulating: "Weldon suggested that crabs with a narrow frontal breadth could filter muddy water more efficiently and were therefore more likely to survive under these conditions" (Ibid. p. 306). He imitated the real case in the laboratory by keeping crabs in muddy water and measuring the death rates of narrow and wide types. He showed that the death rate of wide type was significantly higher than the narrow type (Ibid. p. 307).

Weldon's study, even if it has many flaws, was important for some reasons. It was flawed because he hadn’t controlled for the alternative hypothesis that variation in the death rates resulted from differential growth rates. More specifically, it might have been the case that the crabs with wide frontal breadth had developed faster due to a purely environmental cause, thus, they were younger and less resistant to the muddy water treatment (Ibid.). Thus, there might have been no selection at all.The

study was still important because, connecting a change in some ecological factor to a change in the composition of a population is one of the hallmarks of evolutionary biology. Doing this in a quantitative manner and testing the connection by means of an experiment made Weldon's study very important in the development of evolutionary theory. In addition, this study was one of the first studies in which natural selection was seen in action and in nature, not in some laboratory setting: "“we have here a case of Natural Selection acting with great rapidity, because of the rapidity with which the conditions of life are changing” (Weldon 1898, cited in Bulmer 2003 p. 307).

Weldon was a critique of Mendelian genetics throughout his life. He thought that the law of segregation conflicted many observations. He believed that complete dominance was an essential part of Mendel's laws, which was not the rule but the exception for many heritable characters. But the worst fault he saw in Mendelian genetics was *neglecting ancestry.* To understand the last criticism, a few words about the law of ancestral heredity must be said.

According to Galton’s law of ancestral heredity the correlation values for inherited traits of offspring and ancestors decreases exponentially when one goes to earlier ancestors. For instance, the law states that the correlation of the height of offspring and each parent is nearly ½ and the correlation value for grandparents is ¼. The correlations constitute a series such as "x0= ½ x1+ ¼ x2..." where x0 is the offspring phenotypic value and x1, x2,... refers to the phenotypic values of ancestors. These correlations were interpreted by Galton and Weldon as real contributions of ancestors, not simply as information useful for prediction. In other words, Weldon and Galton believed that the hereditary constitution of an individual is a mixture of the hereditary constitutions of its parents, grandparents, so and so forth, with each earlier generation making a diminishing contribution.

In Mendelian theory, knowing the genetic constitution of parents is adequate in the prediction of possible types of offspring. For instance, if a phenotypical trait is influenced by a pair of alleles *A* and *a,* and parents are known to be homozygous for

A and *a*, the offspring will all be *Aa*. The F2 cross between heterozygotes will give the 3:1 ratio. The recessive factors are carried to the recessive homozygotes intact. Their coming from a heterozygous or homozygous ancestor, which differ for the phenotypical character measured, doesn't influence what phenotypes they will lead to in later generations. The origin of the alleles - their ancestry - has nothing to do with the resultant phenotypes. This is why Weldon criticized Mendelians for neglecting ancestry.

Karl Pearson, on the other hand, never saw the ancestral law as expressing the real physical contribution of early ancestors to the offspring (Bulmer 2003). For Pearson, the law of ancestral heredity was merely a mathematical tool for predicting phenotypic values of offspring from a knowledge of the phenotypic values of ancestors. Pearson, in his reply to the Mendelian claim that the knowledge of parental genotypes is adequate, revealed an important insight of the biometrical school: if one is "to predict phenotypes on a basis of phenotypes, then knowledge of phenotypes of ancestors more distant than the immediate parentage would be advantageous" (Norton 1975a, p. 544). This insight is important if it is thought with the methodological tenets of biometry. Biometry deals with observable properties, their values and correlations. This is different from the Mendelian framework in which genotypes - the set of genes possessed by an individual - determines its phenotype. Galton's theory of "stirps" contained some concrete assumptions about the mechanism of inheritance. But Pearson's interpretation of biometry was independent of the specific models proposed by Galton. He just searched for the most general laws that would describe and predict empirical data about inheritance phenomena, as it could be derived from phenotypic measurements.

Karl Pearson's philosophical tenets are important in understanding his position in the debate. If we are asked to place Pearson on the scale of positivism and realism about theoretical entities, he certainly lies closer to the positivist side. Pearson, just like Ernst Mach, interpreted theoretical entities as useful summaries of observational knowledge. Their main function was determined by the role they played in the

economy of thought. Economy of thought is one of Mach's central concepts. In short, it is a general principle which determines the efficiency of organizing observational knowledge. The Mendelian gene and the Mendelian theory of inheritance would be evaluated according to this principle. Are they good at organizing and summarizing what is known observationally? According to Pearson, the domain of applicability of Mendelian laws was limited (Norton 1975b, p. 89). They were limited to cases where segregation and dominance were complete. Those laws were inapplicable to continuously varying heritable traits. Thus, Mendelian laws weren't successful according to the principle of the economy of thought. Pearson, just like Weldon, thought that Mendelism and Biometry were irreconcilable because he believed that complete dominance and "a few genes for a trait" perspective were irrevocable principles of Mendelism.

The attempts to reconcile biometry and Mendelism gave its first fruits in 1902. Udny Yule (1902) is the first scientist who stated the multifactorial hypothesis for continuously varying characters. According to Yule, if there are many factors with two alleles for a trait, even if the replacement of each allele is a "discrete step" at the genetic level, the observable influence would be indistinguishable from continuous variation (Norton 1975a p. 542).

Pearson, in 1904, showed that n pairs of factors acting additively on a character, could lead to a normal curve even under the assumption of complete dominance (Norton 1975a, p. 543). But in this scenario, the correlation between each parent and offspring was approximately ⅓, while biometricians had calculated a value around ½. Thus, aside from methodological differences, there was a *significant numerical disagreement*.

Yule (1906) was again the first one to realize that allowing for incomplete dominance will raise the correlation values to the empirically obtained values. But Pearson, seems to have believed that complete dominance was a *sine qua non* of Mendelian practice. He suggested Yule to discuss whether incomplete dominance was acceptable with the Mendelians (Norton 1975a. p. 544).

Pearson was already aware that Mendelians had observed cases in which dominance was incomplete. But in every occasion he criticized Mendelism, he considered complete dominance as an essential assumption of Mendelism. The real issue lied in methodology. After encountering many suggestions of a theoretical reconciliation (e.g. Yule's 1902 and 1904 papers, his own 1906 and 1909 papers), Pearson was still unmoved. In his referee report about Ronald Fisher's attempt for a theoretical derivation of biometrical generalities from a Mendelian framework, Pearson said that the Mendelian multifactorial explanation was one of the *many possible explanations* for those generalities, and Mendelian laws were only valid for limited set of hereditary phenomena (Norton and Pearson 1976). Probably, Pearson was more interested in the width of applicability (i.e. generality) and sufficiency in empirical description than the metaphysical status (e.g. whether the theory proposes discrete particles or not) of a theory. In this regard, Mendelism must have seemed to him not economical: it wasn't general enough to gather all inheritance phenomena under simple observational laws. Incomplete dominance and multiple factors were seen by Pearson as *ad hoc* contraptions which made the theory more complex than the original form. Even with these modifications, Mendelian genetics in practice couldn't study traits whose genetic basis consisted of many genes.

Even when a theoretical explanation of continuous variation was given in the Mendelian framework by Fisher in 1916[81], Pearson pointed to the differences between Fisher's purely theoretical assumptions (i.e. there are indefinitely many genes influencing the trait) and the working assumptions of experimental genetics. Pearson noted, in his referee report on Fisher's famous paper, that

[81]Fisher sent his paper, in which he reduced biometry to Mendelism, at first (1916) to the Annals of the Royal Society in London. The paper was evaluated by Karl Pearson and Reginald Punnett. It wasn't published there, so he got it published in the Annals of the Royal Society of Edinburgh (1918).

> There has been a tendency recently among Mendelians to approach the biometric standpoint by increasing to two or even four the Mendelian units involved in the case of any character, but I am unaware that any Mendelian would admit of an indefinitely large number; in fact it would carry the character out of the range of experiment by Mendelian methods (Pearson K. 1916, reprinted in Norton and Pearson 1976).

That was what Pearson saw in Fisher's paper. Looking back from the 21st century, what did Fisher achieve in his "Correlation between Relatives on the Supposition of Mendelian Inheritance"?

Pearson (1909) had shown that in a Mendelian population where multiple genes influence a phenotype (e.g. stature) and pairs of alleles show complete dominance, expected correlation between midparent value and offspring value will be 1/3 but the correlation calculated by biometricians was nearly ½.

Fisher's first task in his 1918 paper was to explain this discrepancy away. He developed a model in which:

a. Indefinitely many factors (genes) influence a character.
b. Their effects are infinitesimal.
c. Factors at different loci act in an additive fashion.
d. Dominance between two alleles on the same locus can take any value between complete dominance to no dominance.
e. Factors obey Mendel's laws of transmission (they segregate independently).
f. There is no assortative mating in the population.

If the contribution of every allele is infinitesimal, the sum of different alleles will give a normal distribution according to the central limit theorem. Fisher concluded that if the contribution of each allele on an individual's deviation from the population mean is infinitesimal, their sum will give the total portion of heritable variation for that trait. Under these assumptions, Fisher calculated the correlation values and it appeared that they are in good agreement with the values obtained by biometricians. The discrepancy was a result of Pearson's assumption of complete dominance.

This paper is a milestone in population genetics literature because it was the first *general* demonstration of the consistency between Mendelian genetics and continuous variation. Yule's (1902, 1906) papers demonstrated the same points under more strict conditions such as the frequencies of alleles were ½, dominance was incomplete for all alleles and there was no linkage. In Fisher's paper, there is a place for dominance, frequencies need not be ½ for each allele and linkage (he calls it coupling) doesn't affect the results.

As we already saw in Pearson's remarks, numerical agreement didn't mean so much to the biometricians. Pearson (1916) opposed Fisher's claims on two grounds: His assumptions were not shared by experimental geneticists and even if they were shared, they could not be tested. There are many other possible models in which the observed correlation values will be obtained so there is no need to accept this model at face value. The numerical agreement had been traded-off for empirical adequacy.

Pearson was right about two points: This model was not testable by the experimental methods of Mendelism of that day and many other possible models could have been developed in accordance with the data. First of all, the assumption of indefinitely many genes affecting a trait was not realistic. This could have been replaced by a model in which there are, say, dozens of genes affecting the trait. In such a model, normal distribution and correct correlation values could still be obtained. But it was impossible in 1916 to search for dozens of genes in usual experimental setups used by Mendelians (i.e. hybridization).

Fisher (1922) was well aware of the difficulty in experimentally verifying the hypothesis of indefinitely many genes influencing a character. But he was more flexible than biometricians. For him, the important point was that, even if Mendelian analysis of large-effect mutants hasn't been successful in economically valuable characters (e.g. milk yield, crop size and number, etc.) it was still possible to "fall back upon statistical methods, and recognize that if a complete analysis is unattainable it is also unnecessary to practical progress" (Fisher 1922, p. 322). In short, Fisher meant that in the absence of an explicit Mendelian model - i.e. a model

that contains the genes, their chromosomal positions, their specific effects and their frequencies - methods of biometry would be still useful in breeding studies.

Biometry, as an independent discipline, didn't live a long life. But its techniques, some of its concepts and most importantly its spirit - quantitative analysis of variation - lived to date. What united Fisher and biometry was their eugenic ambitions, their belief in the high heritability of most biological characters and their belief in the power of statistical techniques in the investigation of evolutionary phenomena.

Fisher was whom the spirit of biometry lived with. Fisher's simplifying assumptions, his genic selectionism, his minimizing the role of epistasis (i.e. gene-gene interactions), gene-environment interactions, turned out to be necessary simplifications to make evolutionary phenomena workable by mathematical methods. The result of this mathematical study was the first population genetic model of evolution. Another mathematical - as well as experimental - geneticist, Sewall Wright, had proposed his model of evolution in 1931. The disagreements between Fisher and Wright illuminate many points about the conceptualization of genes in evolutionary population genetics.

4.3.2 Genes in Evolving Mendelian Populations: The Fisher-Wright Debate

The first phase of evolutionary synthesis consists of the development of mathematical models of genetic changes in Mendelian populations. The most important contribution was the demonstration that even a slight selective advantage could drive evolution if enough time is given.[82] The models were developed by Ronald Fisher, Sewall Wright and J. B. S. Haldane. We will consider only Fisher and Wright here because their dispute clarifies many points about how genes and their effects are conceptualized in evolutionary genetics.

[82]Effective population size is also an essential parameter for the effectiveness of natural selection.

Fisher (1922) set out the first attempts at unifying Mendelian genetics with evolutionary biology. His null model was Hardy-Weinberg equilibrium, which states that gene frequencies don't change in the absence of selection, mutation, migration, non-random mating, etc. Fisher (1922) added the effects of selection, dominance, mutation, heterozygote superiority, random extinction of genes, non-random mating to see how gene frequencies would evolve under these assumptions.

Fisher showed that homozygote superiority leads to the fixation of one allele. The important point is that, in Fisher's model, both *aa* and *AA* were superior to *Aa*. If the fitnesses of the three genotypes satisfy the relation *aa=AA>Aa*, then the allele which will be fixed depends on the initial frequencies. In the case of heterozygote superiority, a stable polymorphism is reached. In such a case as *aa=AA<Aa*, the equilibrium frequencies of alleles will be 0.5 respectively.

In Fisher's model, natural selection in a Mendelian population consisted of differential reproduction of certain alleles. New alleles arise by mutation and mutation itself is an infrequent phenomenon. Emergence of a beneficial mutant allele is much less probable, but given that it happens, what will the fate of the new alleles be? For rare and fitter (i.e. beneficial) mutations to gain a foothold in a population, Fisher showed that population should be large so that the absolute number of mutants should be high. Otherwise, chance extinction is more probable than fixation by selection.

Fisher was a panselectionist and Newtonian reductionist. He was panselectionist because he believed that natural selection acting on single genes is the most powerful source of evolutionary change. He was a Newtonian reductionist because he believed in the following:

1. The Fundamental Theorem of Natural Selection is like Newton's laws of gravity. It is simple, elegant, universal and explanatory.
2. As the theory of gases explain certain behavior of gases by just taking into account their statistical properties – omitting the nature of individual gas

molecules – population genetics can explain evolution by the statistical distribution of genes (Fisher 1922, p. 209).

3. But for such a reduction to be feasible, some simplifying assumptions should be made. Population should be extremely large, epistasis should be negligible. Under such conditions, selection acting on single genes is the "supreme determinant of the evolutionary process" (p. 209).

Fisher was thinking more like a mathematician than a biologist. Fisher (1930) claims that training in mathematics and training in biology influences the imagination in such a way that mathematicians have the advantage of thinking about possible objects whereas biologists are more constrained by the actual. He cites Eddington's phrase to make his point: "We need scarcely add that the contemplation in the natural science of a wider domain than the actual leads to a far better understanding of the actual" (1930, viii).

In contrast, Sewall Wright was trained as an experimental biologist. Wright's theory is influenced by his laboratory genetics work with William Castle on hooded rats and his breeding work. It incorporates more biological assumptions than Fisher's. Their disagreements about evolution were not about the formal techniques used or numerical results obtained (Provine 1992). The differences lie in the biological assumptions about how evolution occurred on earth.

In Wright's shifting balance theory, for natural selection to produce significant results in short periods of time, populations should be small enough for random drift to carry them from an adaptive peak to a higher peak. If, as Fisher suggests, populations are very large and there is random breeding, this problem doesn't arise because fitness landscape has a single peak and adaptation reduces to climbing to that peak. Wright's shifting balance theory predicts that small semi-isolated subgroups will make selection more efficient. Random drift is the force that pushes a species into the valley till it reaches the shoulders of another mountain. Natural selection is the guiding force in hill climbing but random drift and the structure of the adaptive landscape produces the discontinuous patterns we see in the fossil record.

The master debate between Fisher and Wright concerned the effective size of evolving populations. For Fisher, in the long run, whole species can be considered as a single population because there is no absolute barrier against gene flow in a species. Fisher's insistence on large populations depends on the idea that the larger a population, the more variable it is and the more variable it is, even the slightest advantages (i.e. slightest fitness differences) can be exploited by natural selection. In his (1922) own words:

> In all cases it is worth noting that the rate of mutation required varies as the variance of the species, but diminishes as the number of individuals is increased. Thus a numerous species, with same frequency of mutation, will maintain a higher variability than will a less numerous species: in connection with this fact, we cannot fail to remember the dictum of Charles Darwin, that "wide ranging, much diffused and common species vary most" (p. 417).

Wright believed that an effectively breeding population is much smaller than what Fisher imagined. As I said, he thought that natural selection is most effective with partially isolated populations of small to moderate size.

Fisher, in contrast, believed that the effective size (effective in the sense that every genotype can potentially mate with every other genotype) is the whole species. There is no absolute barrier if we consider diffusion (i.e. migration). Wright also didn't see isolation as absolute. Local and imperfectly isolated populations (i.e. demes) were enough for genetic drift to rescue a population from the local fitness peak it is stuck in. In addition to this, Wright's theory added a new level on which natural selection can act: interdemic selection. Interdemic selection increases the rate of evolution by selection because it is an additional force of evolution besides selection acting on individuals in a group. In Wright's scenario, the limiting factors would be the local population sizes and the degree of diffusion, not the mutation rate *per se.* The reason is that, although the global rate of mutation is a limiting factor, the selective effect of existing range of genetic variation between demes is more important than the rate of the occurrence of new mutations in each individual.

The second theoretical debate, as documented by Provine, concerned the evolution of dominance. Here, Fisher suggested that slight changes in modifiers accumulate to such a degree that mutant/wild type heterozygotes become more and more similar to wild/wild homozygotes. He also added that even the slightest advantages provided by nearly-neutral and numerous modifier mutants will explain dominance. Like most of his contemporaries, Fisher saw natural selection as an all seeing eye which can discriminate every genetic difference. So, there is no such thing as a neutral mutation, but only "nearly neutral" mutations.

Wright, who was more sensitive to the findings of physiological genetics of his time, said that recessivity results from under-produced (or ill-formed) chemicals from the recessive allele. Wright correctly criticizes Fisher's using nearly neutral mutations as evidence for his theory. He claims that when the effective population size is less than one million, random drift would counteract the selection of nearly neutral variants.

4.4 The Maturation of Evolutionary Synthesis

Fisher-Wright debate influenced the course of evolutionary synthesis, but mathematical geneticists were not the only contributors to the evolutionary synthesis. Stephen Jay Gould (2002) defined the synthesis as the fusion of experimental Mendelism (Morgan style work) with systematics and natural history. Ernst Mayr - a systematist -, Theodosius Dobzhansky - a geneticist - and G. G. Simpson - a paleontologist - were the ones who put flesh on the bones of evolutionary synthesis.

Theodosius Dobzhansky (1937, 1951) is a paradigmatic case in understanding how knowledge coming from diverse areas was unified into a coherent framework. He represents the spirit of modern synthesis (i.e. adaptationism and gene centrism) best and his treatment of diverse possible mechanisms of evolution is the most balanced and fair among his contemporaries.[83]

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[83]Dobzhansky is so fair about the diverse opinions of his contemporaries that even in a text book like *Genetics and the Origin of Species*, he critically evaluates the very radically holistic ideas of

4.4.1 T. Dobzhansky: The Spirit of the Synthesis

If someone asked "what is the spirit of modern synthesis", I would reply that it is genocentrism and adaptationism. Genocentrism in the context of evolution means that evolution is, in the last analysis, a change in the genetic composition of populations.[84] Adaptationism is the view that the most significant factor in this change is natural selection. The combination of the two can be summarized in this dictum: Evolution is a change in gene frequencies brought out, in most of the cases, by natural selection.

In the 1937 edition of Dobzhansky's *Genetics and the Origin of Species,* natural selection was only one of the factors that could bring about changes in the genetic composition of populations, but in the 1951 version, natural selection became the most significant force (Gould 2002).[85] Dobzhansky was a student of Sewall Wright and his ideas on genetic evolution are comprehensible (i.e. qualitative) restatements of Wright's quantitative genetic models. Along with Wright, Dobzhansky (1937) believed that the effective size of a population determines whether selection or drift dominates the course of genetic change in that population. Racial differentiation might be explained totally by nonadaptive forces (Gould 2002, p. 525). This transformation from pluralism to adaptationism is interesting for its own sake but the "hardened" version is more important for our purposes. So, we will continue with the 1951 version.[86]

Goldschmidt as serious alternatives to the more modest genetic interactionism held by most of his fellows and himself. One might compare his attitude against nonadaptive and nongenetic (see his discussion about morphoses and phenocopies) explanations with Mayr's ultra-adaptationism.

[84]We will deal with other aspects of Genocentrism (i.e. its relation to genetic determinism and reductionism) in the last chapter.

[85]Gould (2002) names this general trend as "the hardening of the synthesis". According to Gould, G. G. Simpson's *Tempo and Mode in Evolution* followed a similar trajectory: Initial pluralism about the forces of evolution followed by an adaptationist restructuring of the main arguments of the book in later versions.

[86]Gould (2002) offers a sociological explanation for the hardening. This might be inevitable in the "extrapolation" debate. Extrapolation means that microevolution is not essentially different from

In the 1951 version of Dobzhansky's book, he claims that diversity and discontinuity are both related to adaptation to local environments. Differences in traits (e.g. physiological, behavioral) are due to differences in gene combinations. Adaptive peaks represent fittest gene combinations in a certain local environment and they are occupied by species (p.8). Discontinuity is due to adaptation to discontinuous niches (p. 9).[87]

The first point, that phenotypic differences can be mapped onto genetic differences, is important in understanding Dobzhansky's gene centered view of evolution. According to this approach, the origin of diversity, genetic changes, is transitive from demes to species to higher taxa. This transitivity means that when you look at a static description of organisms on earth, all evolutionarily significant types of variability can be traced back to genetic differences. Thus, the static classification from demes to races and higher taxa depends upon genetic differences (and similarities) and these are "continuous at base" (Eldredge 1985 p. 19). The dynamics of evolution consist of shuffling and reshuffling of what mutation provides.

According to Dobzhansky, species occupy adaptive peaks. Isolating mechanisms were selected to prevent unfit gene combinations being produced. Even the diversity

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macroevolution. The same forces (e.g. selection) that change the frequency of genes in a contemporary population can explain grand scale evolutionary patterns observed in paleontology. This thesis is speculative and some paleontologists like Gould and Eldredge doubt its validity for good reasons. In 1950s, nobody knew whether the differences between, say, vertebrates and invertebrates occurred due to adaptation to different environments. Gould infers from this indeterminacy that there must be more to the hardening than intra-scientific reasons. But I, along with Sahotra Sarkar (2004) prefer to explain this change by means of the growing realization among biologists about the power of natural selection. This does not mean that the genetic basis of changes observed in the fossil record was identified in the period between 1930s and 1950s. Some phenomena which scientist took as prototypical cases on nonadaptive evolution - e.g. genetic drift - turned out to be adaptations. For instance, polymorphism in the coloring and band patterns of the land snail *C. nemoralis* - which had previously been taken as a case of drift - was shown to be the result of selection (Cain and Sheppard 1950).

[87]Dobzhansky sees niches as independent from the organisms that occupy them. He thinks that classification of niches condition the classification of organisms but this looks a bit like a one-way reduction of a two-way relation.

regarding higher taxa is a byproduct of these mechanisms. Thus, the working hypothesis that intraspecific selection processes can be extrapolated to speciation and higher forms of diversification is central in Dobzhansky's viewpoint.

Mutations provide the variation needed in evolution. Dobzhansky (1951) unifies what is known about mutations from experimental genetics with the theory of evolution. But to achieve this, he must first eliminate some prejudices of evolutionists concerning mutations. He relies heavily on the theoretical developments in Morgan's school.

According to Dobzhansky (1951), mutation has two meanings:

> In a wide sense, any change in the genotype which is not due to recombination of Mendelian factors is called a mutation. In the narrower sense, it is a presumed change in a single gene, a Mendelian variant which is not known to represent a chromosomal aberration (p. 28).

In a nutshell, mutation in the broad sense includes chromosomal aberrations such as deletions, reversions, inversions, translocations as well as chromosome number variation (haploidy or polyploidy) and mutations in the single Mendelian gene. The last one is mutation in the narrow sense. One of the foundational assumptions of Modern Synthesis is that mutation in the narrow sense is the most important source of genetic variation in nature.

This classification of mutations reflects the differences in the *causes* that produce genetic changes. Another important classification deals with the differences in the *effects* that follow mutations. The prejudices of evolutionists concern the effects of mutations. As we explained in the section on De Vries' mutation theory, even speciation events could be explained by single mutations. There, mutation was an alternative mechanism of evolution, not just a source of variation. More specifically, progressive mutations could produce new species in a single stroke. Thus, mutations were complex heritable alterations that affected many traits at once. According to Dobzhansky, even if the phenotypical alterations produced by a mutation might be radical, a single mutation can never produce a new species:

> One thing no single mutation has done is to produce a new species, genus, or family. This is because species and supraspecific categories differ always in many genes, and hence arise by summation of many mutational steps. A four-winged mutant of *Drosophila melanogaster* still belongs to that species, although the presence of one pair of wings and a pair of balancers is a character which distinguishes the order of flies (Diptera) from most other insects (see Heitz 1944 and Stubbe and Wettstein 1941). This fact has in the past given rise to the contention that mutations affect only 'superficial' but not 'fundamental' traits. This contention is meaningless because the words 'superficial' and 'fundamental' are not defined. Mutations exist that produce radical changes in embryonic processes, such as cleavage, gastrulation, and organ formation (Poulson 1940, 1945, Gloor 1945, Hadorn 1945, 1948) (p. 31).

What about the mutations examined in experimental Mendelism? These are kind of mutations Dobzhansky sees as the ultimate source of genetic variation. But they occur in laboratory populations which live in much more different environmental conditions than natural populations. Are these mutations qualitatively different from the variation in natural populations? For Dobzhansky, the answer is no but there is some point in the doubts of evolutionists: "The kinds of mutations that one finds depend on the methods of their detection. Since mutations in *Drosophila* have been used chiefly as markers in linkage experiments, emphasis has been laid on easily visible external changes" (Ibid. p. 30). This is why Dobzhansky opposes the view that Mendelian mutations only produce superficial and easily visible changes. The truth is that mutations that affect "fundamental" processes such as physiology and development occur but the methods employed by experimental geneticists could only detect visible changes.

Another idea Dobzhansky refutes is that laboratory mutants are freaks of nature. The challenge is that, laboratory mutants seem to be freaks which have so low fitnesses that they can't live in nature, thus, studying laboratory mutants is useless in understanding evolution in the open. Dobzhansky replies to this challenge by

showing that even in wild populations, there exists an enormous number of concealed recessive lethals.[88]

One important reason for doubting the significance of Mendelian mutations in the study of evolution was that these types of mutations seemed to have strong effects on the phenotype. As we summarized in the section on continuous and discontinuous variation, Mendelian mutations were considered to be discrete and radical in their effects and this was taken to be in conflict with Darwin's gradualism. Fisher's infinitesimal model was a theoretical response to this problem, but it was important to demonstrate the occurrence and relative frequencies of different types of mutations in natural populations. According to Dobzhansky, the relative frequencies of mild, moderate and high effect mutations are very important in understanding the mechanisms of evolutionary change. As we said, methods for detecting mutations were very crude and they focused on identifying radical phenotypic transformations which usually involved visible morphological changes, along with a huge loss in fertility. This produced the false impression that all of the mutations have strong negative effects on fitness. Timofeeff-Ressovsky's ClB experiments cited in Dobzhansky's book show that mutations that have slightly harmful effects on fitness are at least 20%.[89]Thus, Mendelian variation does not consist solely of lethal mutations.

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[88]Concealed variation, in modern synthesis, plays the role of directed mutation or "good of the species" type concepts in older evolutionary frameworks. It is the fountain from which adaptive complexity and diversity flows. Dobzhansky solves the apparent contradiction between the variability-reducing aspect of selection and the benefit of adaptive flexibility of a species which will allow it to adapt to new conditions by means of concealed variation (Dobzhansky 1951. p 74). Older approaches supposed that these demands are satisfied by forces acting for the good of the species (e.g. mutations occurring in accordance with a species' needs, mechanism of use and disuse). Concealed variability is a non-teleological and more reasonable assumption, which was later shown to be true.

[89]For ClB experiments, see chapter 1. It is important to remember that Timofeeff-Ressovsky's experimental population was collected from nature.

The resolution of the inconsistencies between experimental Mendelism and evolution came with the modification of both fields. In the period between 1910 and 1926, Mendelians have already recognized the phenomena of linkage and gene interactions. During this period, Mendelians realized that the effect sizes of mutations are distributed on a spectrum. Part of the mutations had high main effects, some moderate and some minor. The spectrum concept also applies to the range of traits affected by a single mutation. In other words, a mutation had varying degrees of effects on different traits. A single mutation could have a strong effect on a visible trait (e.g. eye color), a moderate effect on fecundity and a minor effect on body size. Most genes identified in classical transmission genetics (e.g. *white, vestigial*) have pleiotropic effects. Their names reflect their most prominent effects. This spectrum concept allowed Mendelian genetics to capture natural variation. In the side of evolutionary biology, Lamarckian inheritance and orthogenesis style explanations were omitted.

Genes and their transformation occupied the center stage in the synthesis, more specifically in Dobzhansky's work. Dobzhansky is a paradigmatic case because he made mathematical population genetics comprehensible to evolutionary biologists and because he built the concrete connections between the findings of genetics with the problems of evolutionary biology (e.g. speciation).

Genocentrism is an essential working hypothesis in Dobzhansky's view of evolution. Dobzhansky (1951) defends a strong form of Genocentrism in which, phenotypes are seen as the byproducts of the replication of genotypes. His schematic description of genotypic reveals this point:

A + B = 2A + C

A + B1 = 2A + C1

A + B2 = 2A + C2

"A" is the genotype, "B" is the specific environment and "C" is the phenotype. In this scenario, development is the shaping of environment by the genotype. Genotype is

the active, organizing element in the causal chain whereas environment is an organizing factor only in the historical sense (e.g. in the process of adaptation by natural selection).

Dobzhansky's genocentrism doesn't make him a genetic determinist. Genetic determinism is the view that the genotypic constitution of an organism fixes its phenotypic traits. Dobzhansky (1951) has a subtle, and again a spectrum type view about genetic determination. Flexibility or rigidity of genetically determined traits comes in degrees, according to Dobzhansky. Blood groups stand at one edge whereas human personality and mental capacities stand at the other edge. Human skin color stands in between these extremes. Flexibility and rigidity are themselves determined by the genotype. Development is buffered against perturbations caused by external forces. This is especially true for housekeeping mechanisms. These types of buffering mechanisms are subject to strong negative selection. So, flexibility and rigidity of phenotypes are themselves adaptations (Ibid. p. 24).

The relation between the genotype, environment and the phenotype is expressed in the norm of reaction. Norms of reaction for continuous traits demonstrate the response of genotypes to certain environments. Not all responses of genotypes are adaptive. The adaptivity of the response of a genotype depends on the adaptive flexibility of genotypes and the range of the environmental variable considered.

Dobzhansky distinguishes two kinds of environmentally induced phenotypes: modifications and morphoses. Modifications are environmentally induced variants of a species. They are adaptive responses to environmental changes which are in the normal range of environmental variability. Morphoses are variants induced by abnormal environments and they are usually maladaptive. Thus, morphoses don't correspond to historically shaped, adaptive response mechanisms. Dobzhansky detects Lamarck's mistake in his mistaken belief that these response mechanisms are the driving force of evolution. In fact; these mechanisms are the products of evolution by natural selection.

Genocentrism also doesn't imply genetic reductionism. Since we will analyze the relations between Genocentrism, genetic determinism and genetic reductionism, we will only mention one aspect of Dobzhansky's stance against a crude form of genetic reductionism: unit factor hypothesis. According to this hypothesis, single genes correspond to single traits. This view was already refuted by Mendelians, especially by Morgan.

For Dobzhansky, "gene for X" only tells the difference-making capacities of alleles, not the capacities to create specific traits:

> Genes that produce changes in more than one character are said to be pleiotropic or have manifold effects. The frequency of such genes is not well known. A majority of mutations produce striking changes in a single character, and their manifold effects, if any, involve changes which appear trivial. Thus, the main characteristic of the mutant vestigial in *Drosophila* is a decrease of the wing size. But to conclude that vestigial is a 'wing gene' rather than a 'bristle gene' would be as naive as to suppose that a change in the hydrogen ion concentration is a 'color gene' because it produces a striking change in the color of certain indicators. The mutant as well as the ancestral form possesses alleles of the gene producing the mutation. The phenotype of the ancestral form is, then, determined by the gene *A* in cooperation with all other genes composing the genotype, while the phenotype of the mutant is due to the cooperation of the gene *a* with the same residual genotype. Therefore, the differences between the ancestral form and the mutant are indicative of the effects of the change *A*--->*a*, but not the sum total of the effects of either *A* or *a*. (pp. 33-34).

The perspective is identical to Morgans'. *Gene differences explain phenotypic differences but genes don't explain the presence of biological traits*. This perspective is preserved in modern versions of the genocentric view of evolution, such as Dawkins' (1976, 1982). This is some form of reductionism because the substitution of *A* with *a* is taken to have a specific effect on the phenotype – and consequently, fitness – regardless of the genotypic background, frequencies of the alleles and the

environment.[90] This type of reductionism which is especially prominent in some simple population genetic models of evolution (i.e. single locus biallelic models) has been criticized fiercely by Ernst Mayr. Mayr named this type of theorizing "beanbag genetics".

4.4.2 Beanbag Genetics Dispute

Genetic analysis requires variation. More specifically, Mendelian analysis requires heritable and discrete variation in order to analyze the inheritance patterns of traits. Without differences in phenotypes, it is impossible to unravel the genetic basis of traits. Phenotypic differences Mendelians study have traditionally been discrete. This was mainly because the methods of detection in Mendelian hybridization experiments necessitate discrete phenotypic variants. In the absence of these variants, genotypes cannot be identified and the exact laws of genetic transmission don't work. However, Fisher (1918) had shown that phenotypic discreteness is not a theoretical necessity. What makes a model Mendelian is the discreteness of genetic factors, not discreteness of phenotypes. This theoretical idea by itself doesn't help experimental geneticists so much. It just makes Mendelism consistent with some recalcitrant phenomena such as continuous variation.

The source of heritable variation in Mendelian genetics is mutation. Mutation is a substitution of an allele with another allele at the same locus. Evolutionary population genetics rose on the same ground. Evolutionarily significant variation should be heritable. Mutations in single genes (Dobzhansky's mutations in the narrow sense) provide the most important (i.e. most frequent) source of heritable variation. In this theoretical framework, heritable variation boils down to possessing different alleles.

[90]Falk (1990) calls this type of reductionism "Mendelian reductionism". Mendelians know that no single gene can cause the totality of a trait but they act "as if it is causally determined by discrete 'genes for' the trait" (p. 313).

In population genetics, evolution is a change in the genetic composition of populations. The genetic composition of a population consists of alleles and their frequencies. Thus, the definition can be reformulated such that: "Evolution is a change in allele frequencies". Natural selection, random drift, mutation and migration are the factors that change these frequencies.

Fitness is a key concept in population genetic models of evolution. Selection occurs when there is a heritable variation in fitness. In a Mendelian population, this amounts to:

1) Different alleles at the same locus confer different fitness contributions to their bearers.
2) Fitness differences – along with population size, initial relative frequencies of alleles, etc. – determine the fate of the frequencies of alleles in later generations.
3) Most importantly, in the absence of epistasis (i.e. gene-gene interaction) and gene-environment interaction, fitness of an individual is an additive function the fitness contributions of the alleles it possesses in its entire set of loci.

Do single alleles have stable and context independent fitness values? Can evolution be described as the substitution of these alleles, *one at a time*? The simplification that individual alleles have context – i.e. genotypic background and environmental heterogeneity – independent fitness contributions has constituted historically the major point of conflict between field naturalists and population geneticists. The conflict is named the "beanbag genetics controversy" because in 1959, Ernst Mayr compared allele substitution in population genetic models with drawing or adding beans, with different colors, into a bean bag.

The dispute began in the 1959 symposium of Cold Spring Harbor Laboratory. 1959 was the 100th anniversary of Darwin's *Origin* and many prominent evolutionists had gathered in order to evaluate the developments in evolutionary theory since Darwin. Mayr made a talk with the title "Where are we?"

In his talk, he criticized population geneticists for omitting the complexities of evolution such as the importance of gene-gene interactions in evolutionary change. At the end of his talk, he asked ‘‘But what, precisely, has been the contribution of this mathematical school to the evolutionary theory, if I may be permitted to ask such a provocative question?’’ (Mayr 1959).

Mayr’s criticism of population genetics is summarized in these remarks:

> The emphasis in early population genetics was on the frequency of genes and on the control of this frequency by mutation, selection and random events. Each gene was treated essentially as an independent unit, favored or discriminated against by various causal factors. In order to permit mathematical treatment numerous simplifying assumptions had to be made, such as that of an absolute selective value of a given gene… Evolutionary change was essentially presented as an input or output of genes, as the adding of certain beans to a beanbag and the withdrawing of others (Mayr 1959, quoted in Wright 1960, p. 366).

Mayr reserved a minor role for population geneticists in the 100 year long development of the evolutionary theory. He claimed that their contribution was to revive the trust in natural selection as a potent agent in evolutionary change. Their simple framework was “a necessary step in the development of our thinking” but Mayr believed that it had lost its usefulness because a more sophisticated theory, the “genetical theory of relativity”, was emerging. In this new theory, gene interactions and environmental conditions would be ineliminable factors in computing the fitness values of genes. The units in evolution would be “integrated coadaptive complexes” (Mayr 1959) rather than single alleles.

Mayr’s talk didn’t receive good review from population geneticists. Sewall Wright (1960), who already gave considerable importance to the effects of gene interactions, replied to Mayr’s criticism not only by defending population genetics but also by showing the errors in Mayr’s historiography. Mayr had claimed that in the period between 1900 and 1920, Mendelians were opponents of Darwinism. Wright claims

that this is not the case, at least for prominent Mendelians like William Castle and E. M. East.[91]

Wright, compared to Fisher, gave considerable importance to gene interactions. His idea of an adaptive landscape with multiple fitness peaks is a reflection of the importance of gene combination in determining the overall fitness of a population. The newer population genetics defended by Mayr could already be found in Wright's models: "The 'harmonious' system of genes that characterizes a selective peak is certainly an 'integrated coadaptive complex'" (Wright 1960, p. 370). Thus, Sewall Wright seems not to be a proper target for Mayr's criticism.[92]

Wright (1960) gave examples from his own work, along with Fisher's and Haldane's', to show that gene interactions are not omitted in population genetics. More specifically, in his models, selection acted on multiple alleles in multiple loci (p. 370).

Mayr's criticism involved factual errors about the models he criticized. A more general mistake on Mayr's side, according to Wright, was that he presented mathematical population genetics and "the genetics of natural populations" (such as Dobzhansky's and Timofeeff-Ressovsky's work) as incompatible alternatives. In contrast, Wright believes that there is a division of labor among these two fields of research. One can't do the other's job. The ineliminable role played by population genetics in evolutionary theory is to build bridges between "the bodies of factual knowledge discovered at two levels, that of the individual and that of the population" (p. 371). Population genetics deduces the population level consequences of the individual level mechanisms of gene transmission (Mendel's laws, linkage, polyploidy, etc.).

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[91] T. H. Morgan also changed his opinion against Darwinism in the same period. This suggests that Mayr's historiography is biased.

[92] Mayr (2002) later stated that he was not influenced by Wright's ideas at all because Wright had a mathematical outlook on the phenomena of evolution.

Haldane (2008 [1964]) was more ambitious in his reply to Mayr. Haldane and Mayr were close friends, who disagreed on many points about evolution (Rao and Nanjundiah 2010). Haldane (1964) replied to Mayr 5 years after Mayr's speech. He stressed three important points. First of all, mathematical genetics had not been a vain endeavor without any genuine findings. It was true that mathematical population genetics lacked expository material such as applications of the techniques to real world evolutionary cases. But there were exceptions to this. Haldane (2008 [1964]) cited the case of *Biston betularia* and industrial melanism for which he had developed a successful model. In that model, Haldane correctly predicted that the advantage of dark colored individuals (the differential selection coefficient) could be as great as 50%. The fashionable selective advantage value in 1920s was around 1%.[93]

The second point Haldane (Ibid.) stressed was that mathematics provided a "scaffolding" for framing evolutionary hypotheses. This scaffolding turned quantitative and untestable evolutionary conjectures (Haldane calls them "verbal arguments") into quantitative and testable hypotheses. To defend the importance of mathematical proof, Haldane referred to Newton's defense against the opposition against his theory of gravity. According to Haldane, Newton had to prove that spherical bodies could be considered as point masses in order to refute the thesis that planets would fall into the world or be dispersed into hollow space under Newton's theory. The upshot for evolutionary theory is that, even if verbal arguments make an intuitively clear case for, say, the thesis that natural selection and not the mutation rate is the pacemaker in evolution, it was still necessary to show this conclusion mathematically, in order to persuade the scientific common sense (p. 438). Haldane mocked Mayr's ideas like "coadapted gene complexes" for being vague and untestable.

[93]In theoretical models, small selective values were invoked in order to show that even a slight selective advantage can alter gene frequencies significantly. This demonstrates that selection, however weak, determines the rate of evolution, rather than the mutation rate.

The third and probably the most important point was that population genetics omitted the details of the mechanisms of gene action and interaction for good reasons. In Haldane's (2008 [1964]) words:

> Of course, Mayr is correct in stating that beanbag genetics do not explain the physiological interaction of genes and the interaction of genotype and environment. If they did so they would not be a branch of biology. They would be biology. The beanbag geneticist need not know how a particular gene determines resistance of wheat to a particular type of rust, or hydrocephalus in mice, or how it blocks the growth of certain pollen tubes in tobacco, still less why various genotypes are fitter, in a particular environment, than others. If he is a good geneticist he may try to find out, but in so doing he will become a physiological geneticist. If the beanbag geneticist knows that, in a given environment, genotype P produces 10 per cent more seeds than Q, though their capacity for germination is only 95 per cent of those of Q, he can deduce the evolutionary consequence of these facts, given further numbers as to the mating system, seed dispersal, and so on. Similarly, the paleontologist can describe evolution even if he does not know why the skulls of labyrinthodonts got progressively flatter. He is perhaps likely to describe the flattening more objectively if he has no theory as to why it happened (p. 439).

Haldane's position concerning the status of mathematical population genetics was very similar to that of Ronald A. Fisher. Even if his *Causes of Evolution* included many more possible scenarios of evolution than the simple hill-climbing model of Fisher, he agreed with Fisher on the idea that the details of gene action don't make a difference in the mathematical treatment of evolutionary genetic phenomena. This is a common stance among population geneticists, not because of a theoretical pretension - such as reductionism - but the model building process in population genetics forces them to abstract away the details of gene action and *interaction*.

4.5 Constructing Population Genetic Models of Selective Evolution

The model building process in population genetics begins with the simplest assumptions, such as two alleles at a locus with fixed, frequency independent relative fitnesses, random mating, etc. If the predictions of the simplest model fit well with the data, there is no need to add any other factors. But when prediction deviates significantly, those complicating factors ignored in the initial model are added so as

to make the model more realistic (Sober 1993).[94] This process of adjustment is called model fitting: if the model predicts data better than the null hypothesis, then it is worth following. Since the null hypothesis is almost always false, it must be replaced by the simplest alternative that accounts for the data.[95] If a more complicated alternative model predicts the data better, it would be pursued. For instance, a single locus biallelic model of selection in a diploid organism begins with frequency independent, fixed fitness differences between alleles and it is aimed at deriving the changes in gene frequencies in a real evolutionary setting. It is contrasted to the null model, which is usually the Hardy-Weinberg equilibrium. Under the assumption of random mating and no evolutionary force, the frequencies of alleles are not expected to change. This is why it is called an equilibrium state. For instance, if the population contains allele *A* with the frequency *p* and allele *a* with the frequency *q*, the frequencies of each genotype in the second generation would be p^2 *(AA):* $2pq$ *(Aa):* q^2 *(aa)*. From these ratios, the frequency of the alleles can be computed again such as *A:* $(p^2+pq)/p^2+2pq+q^2$ which simplifies to *p* given that $p+q=1$. But if the frequencies are changing, there must be an explanation for it. Frequencies might be changing due to any one of the forces of evolution, such as drift, selection, migration, mutation or a combination of multiple forces. Suppose that the only force acting on the population is selection. This means that one of the alleles is increasing in frequency and the other is decreasing with a certain rate. But how is the rate of selection quantified? Haldane (1932) offers this simple formula: for each generation on average, if the ratio of $p/q=r$ increases to $r(1+k)$, then *k* is the coefficient of selection. The formula does not imply that there is a fixed fitness advantage of *p* over *q* but it implies that, if the change in the ratio is *averaged over multiple generations*, the derived value of increase can be used to estimate the evolutionary trajectory of a population. However, the coefficient of selection by itself cannot determine the fate of a gene in a population. Its form of

[94] See Hartl and Clark (2007) for sample models.

[95] See Meehl (1967) for the inadequacies of statistical methods that depend on null-hypothesis-signifcance-testing. This paper was specifically written for soft (nonreplicable, non-experimental) areas of psychology, but is relevant to genetics as well.

inheritance - whether it is dominant or recessive, whether its absolute number is small or large, whether it is autosomal or sex linked - will influence the number of generations needed for a significant change. For instance, dominants with a selective advantage will increase more rapidly than recessives, as shown by the dark mutation in the famous *Biston betularia* case (Ibid. p. 98). *B. betularia* is a species of moth whose dark form replaced the lighter form in Britain in the 19th century. The dark form, *Biston betularia f. carbonaria* was fitter than the lighter form because it could avoid predation by birds, due to the camouflage advantage its dark color provided in an environment where industrial pollution made its resting places - trees - darker.

Natural selection can also be represented by relative fitnesses. This requires that the Hardy-Weinberg equilibrium is modified according to the fitnesses of each genotype. Fitness, or more correctly relative fitness, is the ratio of viabilities of each genotype divided by the viability of a standard genotype (Hartl and Clark 2007, p. 207).[96] Viability refers to the probability of the survival of a genotype to the reproductive age. The choice of standard genotype is arbitrary, but usually, the one with highest absolute viability is taken so that the highest fitness is 1 (Ibid.). The mean fitness of a population is the total fitness of all genotypes, weighted according to their frequencies in the population. Suppose that the fitness of AA is w1, fitness of Aa is w2 and fitness of aa is w3. Further suppose that the initial frequencies of genotypes are p^2 (AA) : 2pq (Aa) : q^2 (aa). Then, the mean fitness would be $p^2w1+2pqw2+q^2w3$, which is abbreviated as w. The frequencies of alleles *after selection* would be $p'=(p^2w1+pqw2)/w$ and $q'=(q^2w3+pqw2)/w$ respectively. From these equations, the change in the frequencies of each allele and each genotype can be calculated, for any number of generations. If w1=w2>w3 or w1>w2>w3, in a certain number of generations, the whole population will consist of AA individuals. If w2>w1 &

[96] There are many different definitions of fitness. Dawkins (1982) counts five of them. The term used in this chapter corresponds to his second, population genetic concept of fitness (Ibid. p. 182).

w1>w3, the case of heterozygote superiority, the population would reach an equilibrium frequency depending on initial frequencies and relative fitnesses.

The model given above assumes many things such as fixed, frequency independent fitnesses, random mating and that *selection acts only at a particular locus*. This is evident from the formulation of the problem itself: the genotypes whose frequencies are traced are represented at only one locus. The original concept of genotype was defined as the sum total of all genes (Johannsen 1911). In practice, it is impossible to keep track of variation at every gene so, *partial genotypes* are the basic building blocks of population genetic models (Lewontin 2011). Selection acting on a single locus is not realistic, not even for experimental populations: "An important consideration for any experiment dealing with natural selection in the laboratory is that not all variable can be measured, and other unobserved loci are probably under selection too!" (Hartl and Clark 2007, p. 211). In the case of selection acting on multiple loci, the number of partial genotypes increases, thus, the number of relative fitnesses assigned to each genotype increases. In those cases, it is better to keep track of the fitnesses of *alleles* rather than genotypes. At this point, another simplification is made: the fitnesses of genotypes carrying a certain allele are averaged. The resultant value is called the marginal fitness of an allele, and if it is greater than the mean fitness, that allele will increase in the population (Ibid. p. 224). The biological meaning of the last statement requires some clarification.

Marginal fitness concept is a descendant of Fisher's *average excess*, which is defined like this:

> Let us now consider the manner in which any quantitative individual measurement, such as human stature, may depend upon the individual genetic constitution.We may imagine, in respect of any pair of alternative genes, the population divided into two portions, each comprising one homozygous type together with half of the heterozygotes, which must be divided equally between the two portions. The difference in average stature between these two groups may then be termed the average excess (in stature) associated with the gene substitution in question (Fisher 1930, p.30).

The average excess is *the average phenotypic difference* between the *total set* of genotypes that carry the allele and those that don't. Fisher (1930) considered the case of height but fitness can also be seen as measurable phenotypic property, whose differences might yield the average excess in fitness. For instance, if the genotypes are GG, Gg and gg; and their fitnesses are i, j and k; and their frequencies are P, 2Q and R the average excess is calculated by the formula: $(Pi + Qj)/(P + Q) - (Qj + Rk)/(Q + R)$ (Fisher 1941). It is a weighted average in the sense that the fitnesses of genotypes that carry that allele are counted according to their frequencies in the population. The relation between average excess in fitness and marginal fitness is that average excess is the difference between the marginal fitness of an allele and the average fitness of a population.

The idea of marginal fitness provides a very useful simplification, especially with respect to gene-gene interactions. An allele can have differing effects on fitness, depending on the alleles at other loci. For instance, suppose that a new allele, D, emerged by mutation in a population consisting of such genotypes: AAdd, Aadd, aadd. Further suppose that the new allele found its way into these genotypes such that the population now includes the new genotypes AADD, AADd, AaDD, AaDd, aaDD and aaDd. It might be the case that this new allele increases the fitness of AA and Aa genotypes but decreases the fitnesses of aa genotypes. The marginal fitness of this allele is its average contribution to fitness differences and if, on average, it has a positive contribution, it will be selected and its frequency will increase.[97]

[97] If the fitness of an allele depends on which genotype it occurs, as in this case, any factor that influences the change in frequencies of alleles at other loci will also affect the trajectory of this new allele. The theoretical assumption behind the single gene perspective is that we would have a precise measure of the fitness of an allele iff we have at hand all the possible combinations of genotypes along with their probabilities of occurrence and all environments along with the probabilities of each genotype encountering those environments (Fisher 1930). These strict , purely theoretical requirements for statistical precision can be replaced by a complete knowledge of actual genotypes and experimental control over environments in the case of experimental populations (Ibid.).

4.6 The Gene in Population Genetic Models of Evolution

The gene in population genetics owes much of its content to the Mendelian gene. Genes in Mendelian genetics were difference makers with respect to phenotypic characters. Genes in population genetics are also difference makers, not for a concrete phenotype such as eye color but for the abstract phenotypic value called fitness. Fitness is an abstract phenotype in the sense that it denotes the probability of survival or reproduction, *regardless of the specific ways in which these happen.* This certainly doesn't mean that fitness differences between genotypes has no specific biological reason. In specific models of selection this is apparent. For instance, a model that explains the presence of the sickle cell anemia allele in a certain population should refer to the mechanism by which this normally defective allele can protect its bearers from malaria infection. But *fitness in general* cannot be reduced to the sum of such specific mechanisms (Sober 1993). With respect to the concept of gene, this implies that the gene of evolution is unit of hereditary difference that makes a difference - either positive or negative - on the abstract phenotype called fitness.

Genes in population genetic models are theoretical constructs that keep track of evolutionary changes. Here, the gene is defined by its bookkeeping function, not its causal role in the process of evolution (Gould 2002). But there is a view of evolution, namely gene selectionism, which represents genes as the ultimate *units of selection*, and hence, adaptive evolution.

The units of selection debate concerns the question "What kind of entities does natural selection act on?" The possible answers range from the whole species, groups and individuals and genomes to single genes. These units need not be exclusive, selection might act on all of them. Since species selection is not considered as a reasonable option, and the conditions of group selection would make us digress from the subject of gene concept, it is better to focus on "individuals vs. genes" as units of selection.

Gene selectionism, as developed by Williams (1966) and Dawkins (1976), states that the *ultimate* unit of selection is the single gene. Williams (1966) describes the view as such:

> Natural selection arises from a reproductive competition among the individuals, and ultimately among the genes, in a Mendelian population. A gene is selected on one basis only, its average effectiveness in producing individuals able to maximize the gene's representation in future generations. (p. 251).

In this view, genes need not, and usually do not, interact with the environment independently. In other words, the reproduction of genes is mediated by the reproduction of the organisms they reside in. For instance, an allele that increases the running speed of deer increases in frequency only if those deer outreproduce their competitors by means of better predator avoidance. In this case, the selective advantage - namely, the differential success in the solution of the environmentally posed problem of predator avoidance - is not an intrinsic property of the genes, because alleles don't run faster than other alleles, but individuals do. But, as the word "ultimately" suggests, the whole process of competition among individuals, which interact with the environment and which are subject to the forces of selection, can be reduced to the differential reproduction of single genes.

Gene selectionism was justified on the grounds that genes are the only entities that are "immortal" (Dawkins 1976). Immortal means that genes are stable for the long time periods needed for evolution by natural selection to occur. This stability does not follow from a structural property of the DNA. It results from the fact that genes are replicated very faithfully, for thousands of generations. In addition, any change that happens on the structure of genes would also be replicated and this would be the basis of cumulative evolution. In this scenario, individual organisms are "vehicles", built by the genes in order to replicate themselves. So, the individual organism is an ephemeral being, a middleman between the genes in one generation and the next.

Individual selectionism is the view that individuals are the proper units of selection, because they interact with the environment and they reproduce. So, adaptations are

for the sake of individuals that carry them, not the genes which provide the hereditary basis of them. The disagreement over gene selectionism and individual selectionism depends on the relative weights attributed to interaction with the environment versus faithful replication. Interaction necessarily involves a working organism, thus, those who prefer interaction with the environment as a definitive property of units of selection would lean towards individuals, and those who focus on faithful replication would prefer genes.

The idea of gene selectionism is related to the definition of evolution as a change in gene frequencies. In population genetic models, the population is represented as gene pool: the total set of all Mendelian genes in a population of sexually reproducing organisms. Thus, evolution by natural selection is represented as a change in gene frequencies driven by fitness differences between alleles. At first sight, it seems natural to infer, from this description of evolution, the conclusion that single genes are all that matters. In other words, single genes are the causal agents that bring about the changes in their own frequencies. But the gene pool, and the "change in gene frequencies" concepts need not be interpreted in that manner. Selection acts on the population of individuals, it changes the distribution of phenotypes and this change is *reflected in the gene frequencies*. That is, the individual organisms with their phenotypes are the true causal agents in evolution, but the *consequences* of evolution can be represented as the changes in allele frequencies. This bookkeeping account of S. J. Gould (2002) is the exact opposite of gene selectionism because in this account, genetic changes are records of evolutionary changes. The problem with this account is that genetic changes don't merely keep track of the changes in phenotype distributions. They cause those differences, regardless of the complex nonlinear causal paths from genes to phenotypes, and this fact cannot be detached from the theory of evolution, without abandoning what has been learnt through the progress in population genetics. A more moderate view would be that the effects of single gene substitutions acquired a central place in population genetics because of methodological reasons - mostly for the sake of making evolutionary phenomena amenable to mathematical study - and these reasons were later turned into the

reductionist thesis of gene selectionism. Genes are neither bookkeepers nor the exclusive units of selection. They are difference makers with respect to phenotypes of individuals, which results in the differential survival and reproduction, and hence, the selection of types of individuals.

4.7 Conclusion

In this chapter, the history of the Modern Synthesis was told, with a specific emphasis on the role of the gene concept played in the process. Darwin's theory of evolution by natural selection required that selection acted on minor differences, mostly of the continuous sort, and this apparently contradicted the discrete genetic differences studied by Mendelians. In the period between early 1900s and 1918, Mendelian geneticists developed a new conceptual framework that allowed them to capture continuous variation in a Mendelian framework. The new framework had moved away from the early unit character view to a more interactive view about the relations between single genes and phenotypes. Beginning from Fisher's 1918 and 1922 articles, evolution became a subject of mathematical analysis. The first population genetic models of evolution were constructed. All of these models depended on Mendelian principles.

Genes of population genetics were the genes of Mendelian genetics, but in the new context, they were being used to track the dynamics of evolutionary change in populations. Population genetic models represented the evolutionary process as if all that happened in evolution was the gradual replacement of one gene with its alternative. Simplifying assumptions, which were necessary in the model building process, were later transformed into the reductionistic vision of gene selectionism. In that vision, organisms were seen as vehicles of genes making more of their copies. Genes were represented as entities with their own interests. Natural selection was represented as a process acting on individual genes, optimizing each independently.

These methodological simplifications lead us to the question of why and how genetics progressed in the last century. The answer of this problem is important both for the

philosophical problem of scientific progress and the modern question of whether genetics will be a leading force in future. These points require a reassessment of the history told so far and a fresh look at major theories of scientific change proposed by philosophers of science.

CHAPTER 5

METHODOLOGY

5.1 Introduction

In the previous chapters, I have offered a history of genetics with a specific emphasis on the interaction between theoretical perspectives and the actual problems encountered by geneticists. In this chapter, I will try to show the relation between conceptual change in genetics and philosophical models of scientific progress.

The groundbreaking theoretical ideas such as Mendel's laws, genotype-phenotype distinction, linkage, multifactorial inheritance, the sequence hypothesis, gene regulation and evolution as the change in gene frequencies will be placed into the context of the problems for which these ideas were used in the solution. The scheme of the interaction between theoretical ideas and scientific progress will be described.

The history of genetics is a ripe field to test the theories of scientific change. In the first half of the 20th century, philosophers of science focused on the problems such as how to distinguish a scientific theory from a pseudoscientific one, what the relation is between evidence and a theory, etc. The focus was on theories, the logical relations between observations and theory, the logic and/or pragmatics of theory replacement. However, in genetics, theory is not the focal unit of scientific change.

This is not to say that there had been no grand theories for inheritance, or that such grand theories were completely useless. A grand theory in my terminology refers to a set of propositions which explain the empirical/experimental findings of a domain of science in a comprehensive fashion. Weismann's germ plasm, Herbert Spencer's theory of particulate inheritance, Darwin's pangenesis, De Vries' intracellular pangenesis, Naegeli's idioplasm were all such theories in the 19th century. The problem with such theories in genetics is not their truth or falsity. Many points

expressed by the 19th century particulate theories of inheritance are still deemed correct. For instance, Weismann's idea of the noninheritance of acquired characters or the particulate nature of the genetic material are principles that have survived more than a century. However, partial truth is not the best criterion for evaluating past theories. Leading to progressive research is more important as Mendel's analytic and experimental approach illustrated.

Mendel's theory is not in the same class with those theories. Mendel said nothing about the developmental process or the evolutionary implications of his "laws". In this sense, his work did not brought out an all encompassing theory of inheritance, development and evolution. As a "paradigm" setting discovery, Mendel's work is as modest as one can get. But his experimental method satisfies at least one interpretation of Kuhn's paradigms: it is an exemplar. The reasons for the last statement have been stated in the second chapter. The summary is that Mendel's work acted as a standardized procedure for carrying out genetic work for later Mendelians, despite the fact that their interpretation of such experiments differed from Mendel himself. Mendel had nothing to do with Bateson's unit factor or presence-absence schemes and he knew nothing about the interactions of alleles in the production of phenotypes. He is not a founder of genetics for laying down the theoretical basis of inheritance. He is the founder because he laid down the *methods* of investigating hereditary phenomena. By using those methods, later generation of scientist could investigate developmental and evolutionary phenomena.

The information based viewpoint of molecular biology acts as a grand theory - similar to the 19th century theories - which seems to unite various biological phenomena. However, the prominent molecular biologists' reductionist ideas guided research not because they provided a theoretical vision for *subsuming* diverse phenomena under general laws. They guided research because they directed attention to the mechanism of protein synthesis and other seemingly universal mechanisms such as the regulation of protein synthesis. Eukaryotic genetics is a case against generalizations from prokaryotic genetics but this did not stop molecular biologists in the search for the

genetic basis of eukaryotic phenotypes.[98] This is because, the *methods of investigation* survived, even if the simple theory of gene-protein-phenotype connection was shown to be incomplete.

In this chapter, I aim two things. First one is to connect what has been said so far - the history of genetics - to the general theories of scientific progress. There will be no independent section for the founders such as Kuhn, Popper and Lakatos. Their ideas will be described and criticized "on the go". That is, their ideas will be judged in the context of the story of genetics told so far.

I will begin with history once again. However, I will focus on turning points in the history of genetics. These turning points consist of Mendel's discovery, its unit character interpretation, the multiple factor theory of inheritance, the founding discoveries of molecular biology and the birth of population genetics. Then I will derive some general conclusions about scientific progress in genetics from the history between 1865 and 1960s. In the last section, I will try to assess why genetics became so important for every field of biology.

It has been claimed that modern biological research is gene centered in the sense that genes are privileged in the causal chain of development. I don't aim to give a precise account or a criticism of genetic determinism or gene-centric vision, these debates will be covered in the last two chapters. For this chapter, it is enough to uncover the reasons for privileging genes in biological research. The upshot is that genetics provides analysis tools to gain new knowledge on biologically interesting phenomena.

[98] It is false because there are no "operons" or one to one connections between nucleotide sequences and proteins in eukaryotes. In addition, much of the eukaryotic DNA does not code for proteins but it still has some functions.

5.2 Scientific Progress in Genetics

Scientific progress can be described by many models, depending on the science studied, the cases and philosophical priorities. I offer the following descriptive model.

First, there is a "vaguely" defined problem. Then a method of solution is proposed. This method has certain implications about the domain of the problem. That is, it incorporates some substantive assumptions about the problematic phenomenon. The method - or heuristic - represents the phenomenon very differently from the prior formulation. The method solves this transformed problem. In the meantime, some of the implicit assumptions of the method are made explicit and they are put to test. If they pass, they become core principles, the basis of the theory. Some general principles can get detached from the context of their emergence and begin acting like motivating ideologies.[99] These ideas don't play any explanatory role in concrete cases but they provide a general direction to research and they justify the privileging of this direction against alternatives. A point that should be kept in mind is that in biology, the "vaguely" defined problem never disappears. It haunts scientists even if they are proud of the successes of their paradigm. This latter point is exactly true for genotype-phenotype relation, as we will see in the following paragraphs.

The acceptance of general principles in biology has nothing to do with Popper's crucial experiments or counting the evidence favoring and refuting those principles.[100] In other words, no single experiment can refute them and the value of such principles does not depend on the balance between confirming vs. disconfirming instances. The Popperian "crucial experiment" is not valid for genetics - and probably

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[99] I think the concepts of genetic information and genetic program now act as tools of a motivating ideology rather than well defined concepts of a theory. Well defined, in this context, refers to technical terms whose meanings are directly fixed by definitions, or indirectly fized by the role they play in a formalized theory. In this sense, "genetic information" and "genetic program" are dissimilar to concepts such as Newtonian mass, or wavelength.

[100] Popper (2005 [1959]) describes crucial experiment as an experiment that is conducted to falsify a hypothesis. In this respect, a crucial experiment is a potentially falsifying experiment.

for other sciences as well - because scientists prefer to begin with testing the analytic power of theories rather than testing the truth of the core statements of those theories. Analytical power refers to two related criteria at once: the heuristic power and the explanatory power. Heuristic power of an idea measures its strength in leading to experimental methods to probe the phenomenal domain, and hence, leading to new knowledge.[101] The explanatory power measures the width and depth of explanations that come *after* the experiments are made or the models built.

The latter point, namely counting the confirming and disconfirming instances, is false because not every instance - evidence - is as valuable as any other. There is no universal scale for evaluating the importance of positive or negative evidence. But some evidence is more equal than others. The solution of a difficult problem has greater weight than, say, a replication study.

Those principles prove their worth if they successfully solve *difficult problems.* As Kuhn (1996 [1962]) suggested 50 years ago, what motivates scientists is the difficulty of the puzzles. The difficulty of the puzzles depends on the gap between the paradigm-as-exemplar and the problem at hand. The solution requires ingenuity in devising ways to fill in this gap.

Mendelian genetics exemplifies all parts of the scheme. In Mendel's era, the problem of heredity was mostly a matter about explaining the similarity between parents and offspring. The solution to this problem was sought in embryology and cell biology. The problem, then, was to learn the material structures and developmental pathways that could explain this overall similarity. The germ-plasm, the idioplasm, the stirp were such mechanistic solutions to this puzzle. Mendel came from a different tradition widespread in Central Europe: the hybridizationist tradition. The hybridizationist tradition studied inheritance by breeding experiments. The design of such experiments required discrete heritable differences. The aim in that research was

[101] This is a reading of Lakatos' (1978) general idea about creating new knowledge, adapted to the case of experimental science.

to create new plant varieties by crossing different strains. Hence, even before the famous 1865 paper, Mendel's way of formulating the problem of inheritance was quite different from the developmental or cellular perspectives.

In Mendel's work, the problem of inheritance was formulated as a problem of tracing individual characters which showed discrete differences. The characters and the model organism he chose reflect his preference for clean mathematical generalizations, which he believed to underlie the messy phenomenal world. He represented the problem of inheritance as if it was a problem of combinatorial mathematics. The result was that inheritance was transformed into a problem soluble by controlled hybridization among individuals that have "constant differentiating characters" and finding out the ratios of different types.

William Bateson interpreted Mendel's work as showing that the organism is a collection of dissociable traits. This idea in fact expresses a methodological point of view rather than a metaphysical position. In short, it expressed Bateson's hopes that one day, all heritable traits would be amenable to Mendelian analysis. But Bateson's view could not accommodate the knowledge about the intricacies of gene-phenotype relations. Morgan was an ex-embryologist who knew enough to reject such grandiose claims. Thus, the unit character hypothesis was replaced with the unit factor hypothesis in which Mendelian genes behave as units only in their transmission and not in their effects on the phenotype.These units were deemed constant - except when they undergo mutations - and they were pure in the sense that the alternative versions of a gene did not mix up. The multifactorial hypothesis suggested that many genes could influence a trait and these genes could interact among each other and with the environment in the production of phenotypes. This flexible view allowed Mendelians to continue the search for individual gene variants that cause phenotypic differences while avoiding the ultimate developmental question of how genes determine phenotypes.

In addition, Mendel's law of independent assortment was modified by early Mendelians. The phenomenon of linkage at first appears to be an anomaly for the

Mendelian theory. But Mendelians turned in into an analytic tool to locate genes on chromosomes. This spatial model was supported by cytogenetic studies and it freed Mendelians from the problems of organizing genetic knowledge around a functional/developmental axis. The idea that genes are organized in a linear fashion on the chromosomes and their recombination ratios reflected their positions were soon integrated into the hardcore of Mendelian genetics.

The analytical power of these ideas were put to test when truly anomalous cases were encountered. Gametic purity, or the constancy of genes is a core principle of genetics. Core principles are insulated from refutation in Lakatos' (1989 [1978]) view. This seems to be correct in the case of Mendelian genetics. Castle and Phillips' experiments on hooded rats and Castle's interpretation of the results caused fierce debates among Mendelians. The reason was that Castle's gene contamination/fluctuation view seemed to be an attack on the core principle of gametic purity. In fact, Castle was trying to make room for Darwinian evolvability, without completely abandoning Mendel's principles. There were similar cases such as truncate and beaded characters in *Drosophila.* Mendelians did not interpret these cases as refutations of their paradigm. Rather, they saw them as puzzles that could be solved with some ingenuity. Multifactorial hypothesis was the savior of the gene constancy view. One chief gene plus a number of modifiers as well as recessive lethals could solve the puzzle.

Multiple factor hypothesis (plus gene-gene interaction) acted as a positive heuristic as well as a negative heuristic. It was a negative heuristic because it was used to save the core Mendelian principle of gene constancy. It was a positive heuristic because it allowed geneticists to explain complex, apparently non-Mendelian phenomena. Positive heuristics allow a research program to anticipate future anomalies in a pre-planned fashion and even offer possible ways to handle those anomalies (Ibid. pp. 48-52). The multiple factor hypothesis provided a plan to absorb anomalies, even before the actual cases were encountered.

In the investigations on these puzzles, Mendelians not only saved the hard core of their research program but also invented new investigative methods such as the ClB method. Anomalies were being absorbed while the applicability of genetic analysis was expanding. The period between the rediscovery of Mendel's paper (1900) and 1920s exemplify what scientific progress means at its best.

I've said that the preference to separate the problems of inheritance from the problems of development had transformed the 19th century problem of the developmental mechanisms of parent-offspring similarity. Mendel transformed this problem into the problem of tracing individual characters, or more correctly, character differences. His followers continued from this perspective but this doesn't mean that they have ignored developmental questions altogether. Rather, they investigated development by using the tools of genetics. For instance, they created mosaic Drosophila by transplanting cells from an individual with a certain genetic makeup to another with a contrastive genetic makeup to see what the allele does in a certain tissue. When asked about the developmental effects of genes, Mendelians had a fairly simple answer: Genes determine the inner workings of a cell and this leads to further, organism level effects. Genes were seen as very small particles which directed the developmental process from the nucleus by directing the biochemical reactions in a cell.

The latter idea - that genes direct the biochemical reactions in a cell - turned out to be fertile, although the developmental hypothesis required more time to obtain evidential ground. However, Mendelians till the 1920s worked with multicellular organisms, which made it difficult to analyze the biochemical effects of gene substitutions. In 1920s, it was technically impossible to study eukaryotic cells in cultures. But the area of bacterial and viral biochemistry was providing a new avenue for genetic research. The studies in the period between 1930s and 1940s incorporated the methods of artificial mutagenesis with the techniques of handling those small organisms. The result was the one gene one enzyme hypothesis, which was later transformed into the one gene one polypeptide hypothesis. This hypothesis reflected

a transformation in the problem of gene action. This problem at first was formulated at the level of observable features of organisms. Some pioneers like Muller had pointed to the level of biochemistry and he had prophesied in 1920s that gene action should be related to enzymes. Enzyme function was later shown to be a consequence of the specific three dimensional structure - and modifiable conformation - of proteins.

The structural specificity view became a road worth following only when the macromolecular theory gained sufficient support in the period between late 1920s and 1930s.[102] The alternative view, namely the colloidal theory, depended on the assumption that big molecules were transient aggregations of small molecules and they had emergent properties such as catalysis in virtue of the dynamic interactions between the small constituent molecules. Biochemists knew the biological importance of small molecules such as fatty acids, vitamins, amino acids and their analytical techniques could only handle such molecules without disrupting the structure. Such technical constraints led to the false idea that big molecules could not be stable objects of inquiry. Artificial synthesis of polymers such as nylon, and the application of quantum mechanical theory of covalent bond formation tipped the balance in favor of the macromolecular theory.

The structural specificity view of biologically significant molecules emerged from the physical analysis of macromolecules such as proteins. The idea was that macromolecules performed their specific functions due to the configuration of atoms in certain sites - the active sites. For instance, Linus Pauling had proposed, in 1940s that the specificity of antibody-antigen interactions resulted from the spatial fit between two types of molecules at the binding site of antibody proteins. Crystallography has provided a high resolution picture of protein molecules and it was suggestive of the complexity of this structure. Another line of work that aimed at determining the amino acid content of proteins was being carried out in

[102] Olby 1994.

biochemistry. The advance of analytical techniques such as chromatography were essential in the determination of the amino acid sequence of proteins. Amino acid sequence of proteins was assumed to be the key to their three dimensional structure and hence, their function.

The discovery that DNA is the bearer of genetic information and that it has a double helical structure boosted the advance of molecular biology. These discoveries were surprising, especially the first one, because biologists believed for a long time that genes were made of proteins. The famous "bacterial transformation experiment" was published in 1944 but its importance was not understood immediately. Even after 1953, some biologists such as Darlington were not ready to accept the view that DNA is the material realizer of the abstract entities called genes (Olby 1994, p. 371). The reason was that nucleic acids were for a long time thought to be repetitive - "stupid" - molecules.[103] The techniques to sequence DNA developed much later - around 1970s - than those for proteins. Sequencing the DNA would conclusively refute the idea that DNA is a repetitive polymer with no interesting biological function. But this lack of conclusive evidence didn't stop the founders of molecular biology from assuming a correspondence relation between DNA sequence and protein sequence.

In late 1950s, the problem of gene action underwent another transformation. The one gene one enzyme hypothesis and the biochemical genetics of microorganisms were suggestive of the direction: Genes determine proteins. But how they did this was a mystery. Did genes catalyse the protein synthesis as any other enzyme, did they determine the ultimate functional conformation or else? The sequence hypothesis was a bold answer to these questions. According to the sequence hypothesis, the gene is a piece of DNA whose nucleotide sequence determines the amino acid sequence of a polypeptide. The relation between DNA and proteins is not merely causal - it is

[103] Mukherjee 2016.

informational. If genes had been merely catalyzers in the synthesis of proteins, a gene would be merely one of the causes of the ultimate specificity of proteins.

The central dogma, which was an improved version of the sequence hypothesis, clarified this informational relation. The dogma stated that information could flow from nucleic acids (DNA and RNA) to proteins but not vice versa. In the dogma, information transfer from the DNA to the protein was defined as the precise determination of amino acid sequence of a protein by the precise sequence of nucleotides in a piece of DNA. The problem turned into finding the rules of this translation. The idea of coding was an ingenuous simplification that hastened the solution of the puzzle by reducing the dimensions of the problem. The problem of gene function was transformed into the problem of finding the rules of translation from the DNA (or RNA) words to protein words. However, Crick's attempt to solve this problem by theoretical means alone did not succeed and the code was solved by the in vitro synthesis of proteins from artificial RNAs. The good old biochemistry of protein synthesis, constrained by the theoretical idea of coding, solved the puzzle.

The central dogma played the role of negative heuristics because it blocked the possibility that proteins are the hereditary material and they determined the specificity of nucleic acids. The central dogma prohibited one possible road of research, beginning from proteins and reaching nucleic acids. In other words, it recapitulated Weissman's idea that there is a one-way causal chain in genotype-phenotype relations. What an organism experiences through its lifetime - unless it experiences some mutagenic environments which cause germ line mutations - cannot change what genes it passes to its offspring.

Central dogma was a positive heuristics in the sense that it identified DNA as the source of protein sequence. From the inception of the central dogma, it guided researchers to look for the changes in nucleic acid sequence in order to explain the differences in protein structure, and hence, function. The discovery that sickle cell anemia is caused by a single amino acid substitution and the discovery of the genetic

basis of this disease illustrates the positive role of the sequence hypothesis, which is an essential part of the dogma.

The coding idea had poured a certain informational flavor to the problem of gene function. The idea was that genes carried information for building proteins. But being a static information source for specifying protein structure could not be the only function of the genetic material because, life is a dynamic phenomenon. The metabolic reactions in a single cell could not be modelled merely by referring to a static information source. The operon model and allostery provided the link between static information and dynamic metabolism. These findings led to the genetic program idea which is still a powerful metaphor in explaining the role of genetic material in metabolism as well as development.

In the period between 1900-1950s, problems of evolution increasingly came under the concepts of genetics. The "geneticization" of evolution did not follow a direct route. After the rediscovery (1900), there appeared two interrelated conflicts between genetics and the theory of evolution. Firstly, Mendelians did not believe in the power of natural selection in bringing about the diversity observed in nature as well as the complex adaptive traits of organisms. Secondly, they interpreted discrete mutations as showing that Darwin's insistence upon the centrality of small variations in evolution was faulty.

Both of these anti-Darwinian ideas followed from the practical constraints of early genetic research. That research depended on easily observable phenotypic differences which followed a simple pattern of inheritance. Since geneticists could not detect small effect mutants, their viewpoint was biased towards discrete changes. As the Mendelians learnt more and more about mutations, they realized that genetic variation was much richer and diverse than what they had observed before. They haven't been able to analyze the effects of small effect variants but the presence of numerous recessive lethals and modifiers was suggestive of the hidden genetic variation. This richness of hidden variation hinted at the type of variation on which natural selection could act.

The power of natural selection in creating adaptations and diversity was suspected among Mendelians because the data they had implied that selection could only change the population mean of a character in the population limits. All they had was artificial selection experiments. For instance, from Johannsen's studies, they had learnt that selection had no power to change the mean trait value if the population under study was a pure line. Selection could not create new characters; it can shift the mean value till the genetic variation in a population is depleted. This latter idea suggested that mutation was the ultimate limiting step in evolution: No new mutations, no novelty in evolution. In addition, mutation was believed to be a mechanism of evolution alternative to natural selection. This idea was appealing to Mendelians because their leader - T. H. Morgan - was bored of the speculative theories of evolutionists and De Vries' mutation theory promised to make evolution an experimental area of study.

Mendelians at first welcomed the mutation theory. But in the meantime, they changed its content so radically that the resultant theoretical framework was nothing close to the original version. De Vries believed that organisms entered mutating periods in which new species emerged. Mendelians studied many types of mutations in Drosophila but never observed a single species-creating mutation. Dobzhansky (1951) would later point to this in these words: "One thing no single mutation has done is to produce a new species, genus, or family".

The conflict between Biometricians and Mendelians also revolved around the types of variation. Biometricians studied the inheritance of meristic characters such as height, weight, milk yield. In these characters, it was impossible to point to a few Mendelian factors which can be traced with the usual methods of genetics. Biometricians had developed statistical methods to dissociate the heritable portion of variation from the environmental portion. Mendelians, on the other hand, had to study discrete variation. Biometricians believed that Mendelism was valid for only a handful of inheritance phenomena because it could not explain traits showing

continuous variation. The resolution, once again, came from the multiple factor hypothesis.

Ronald Fisher was not the first scientist who pointed to the reconcilability of Mendelian genetics with biometry. Udny Yule had already demonstrated this under some conditions. But Fisher found a general solution: infinitely many genes with infinitesimal quantitative contribution - given incomplete dominance - would explain the biometrical generalities. The multiple factor theory played the positive heuristic role once again. But this time, it was transformed into a general quantitative hypothesis.

With Fisher's 1918 and 1922 papers, Wright's "Evolution in Mendelian Populations" (1931), a new idea - the Mendelian population - was entering the scene. In Mendelian genetics, population was not an independent object of study. Drosophila were raised in crowded populations for sure, but big populations were merely tools to uncover the genetic basis of trait differences. Mendelian generalizations hold in big populations because the ratios are trustworthy only if the population is big enough. However, the focus is on the individual genetic makeup. Population acts as a microscope that reveals this genetic makeup. The frequencies of these genetic makeups are important only if they reveal crossover ratios or the magic 3:1 ratio.

In population genetics, population is the central object of study. A Mendelian population can be represented as the alleles (or genotypes at certain loci) and their frequency distribution. In its simplest form - the single locus biallelic models - it refers to the frequencies of each diploid genotypes or the frequencies of the alleles. The central question is not what a gene does - or what a gene is - but how these frequencies change over time. Multigenic nature of some traits was accepted in theory, but the field was dominated by single locus biallelic models.

The most important contribution of population genetics to the theory of evolution was to make some qualitative statements about evolution quantitatively tractable/testable. For instance, the idea that weak natural selection was inadequate in bringing about

evolutionarily significant changes could only be refuted if it could be transformed into a quantitative statement. Population genetic models of evolution provided a scaffolding - the essential variables of evolutionary dynamics - in which testable hypotheses could be formulated. Lewontin (2015) summarizes what population geneticists do in practice as such:

> A population geneticist by theoretical training has certain parameters of population change. That's become broadened by the realization that there are between population changes and so on, but within a population we're talking about changes in gene frequency and we have a catalog of the causes: selection, inbreeding, chance, mutation, and so on. Our job as population geneticists is to do the necessary observations of the various things that give us estimates of the strength of those different forces.

Thus, in population genetics, evolution is represented as a change in gene frequencies and "the catalogue of causes" corresponds to the forces that cause this change. This picture of evolution led to gene selectionism, as described in the fourth chapter. For now, it is enough to say that seeing genes as the ultimate units of selection is not a necessary consequence of the population genetic models.

Some evolutionary biologists interpreted evolutionary theory in informational terms. John Maynard Smith, George Williams and Richard Dawkins are some prominent examples of this viewpoint. In short, they claim that genes are information carriers and evolution by natural selection amounts to a natural type of programming which designs the genomes of organisms. This genome contains a genetic program that directs almost everything going on in an organism. This idea explains no concrete case of evolution and it is dubious whether the overall picture of evolution can successfully be captured by such a "bit-by-bit" design scenario. It is also not clear whether information has any unambiguous meaning beyond the domain of DNA-polypeptide relations (i.e. coding). This topic will be covered in the last chapter. For now, it is enough to emphasize that this information based viewpoint was successful in creating a comprehensive rhetoric about the centrality of genes for every subfield of biology. The colorful tales about information should be read as the symptoms of a

process in which genetics permeated all fields of biology. Why this happened will be discussed in the next section.

5.3 Why Genetics Permeated all Fields of Biology

Falk (2009) says that genetics is not an independent research program anymore. Rather, genetic analysis as a research methodology provide a toolset for almost any biological subdiscipline. For instance, evolutionary biology, developmental biology, or any subdiscipline of biology uses the techniques of genetics. May be these techniques, rather than the "fundamental theory" (Waters 2013), which depends heavily on information concepts, is the reason why genetics transformed/invaded all biological sciences. This viewpoint fits well with Waters' (2013) account of investigative pragmatics. According to Waters (2006), the critics and defenders of gene-centrism assume that gene-centrism is a matter of false grand theory which obscures some important facts about core biological processes such as development. But Waters believes that gene-centric biology does not depend on a grand, unifying theory. Gene-centrism is common because "genes are difference makers that can be used to trace and manipulate a broad range of biological processes" (Waters 2013). In an earlier paper, Waters had stated a similar view:

> Gene-centrism dominates because it is organized around an investigative strategy with broad investigative reach. I argue that genes are central to the investigation of a broad range of biological processes not because they figure into a comprehensive theory covering the processes being investigated, but because they provide a useful entry point for investigating and modeling those processes (2006, p. 199).

The contrastive view is that research is organized around a central theory and research consists of solving puzzles, handling anomalies and expanding the reach of that theory into new domains. This understanding of scientific practice revolves around theories. All prominent philosophers of science who search for the dynamics of scientific progress - Popper, Kuhn and Lakatos - had a theory-centered viewpoint.

Popper's falsificationism provides a mechanism of theory replacement in science. Kuhn's paradigms incorporated pragmatic and social elements for sure. But those

pragmatic elements were invoked to explain elimination/replacement of theories. Lakatos' methodology of scientific programs contributed a great deal to the pragmatic element in scientific progress: positive heuristics. Positive heuristics explain why a research program progresses despite the fact that its hard core principles cannot be applied to almost any case that is promised to be explained by the theory. In Mendelian genetics, multigenic inheritance and gene-gene interactions provided such positive heuristics. These points aside, Lakatos' methodology still represents scientific progress in a theory-centered fashion. His research programs are sets of theories who share a common set of core principles. This set consists of revised versions of the theory. Revision happens in the protective belt and it comes from the positive heuristics. The question is whether positive heuristics flow smoothly from the core principles or they come from other sources such as scientific practice. My contention is that they come from practice. But this distinction is not absolute. Core principles of Mendelian genetics - i.e. Mendel's laws as corrected by Morgan's school - are themselves abstractions from the practices of experimental geneticists. What stays invariant under the changes of materials and methods - e.g. model organisms, artificial mutagenesis - are crowned as core principles. In the period 1900-1910, independent assortment was a core principle. In the period 1910-1920, linkage became a core principle as well as a tool to locate genes on chromosome maps. Principles are themselves guides and tools for practice. This is especially true for genetics and this is why no theory-centered view can correctly depict the progress in genetics.

In the philosophy of genetics, the same theory based reasoning is prominent. Both the proponents and the opponents of the gene centric perspective directed their attention to the truth, falsity or the inadequacy of the theoretical framework. The closed system of gene centric explanation – and its critique – will be the topic of the 7th chapter. For now, it is enough to emphasize that genes and their variation do not constitute a comprehensive causal-mechanical explanation of many biological phenomena, but the success of genetics in the last century was not totally dependent upon the descriptive or explanatory adequacy of such a theory. The Mendelian theory

of genes and the early molecular biological concept of information were tied to research traditions which produced much richer knowledge than the direct implications of those concepts.

According to Waters, these theory-centered views are misleading in understanding genetics because they make some very interesting facts about history invisible or marginal. For instance, it is assumed by some historians (Allen, Judson) that the Morgan school's emphasis on distinguishing transmission phenomena from developmental phenomena is an intrinsic part of genetic theory and this idea marginalizes that school's later (1930-1940) work on the developmental effects of mutations by means of mosaicism. Waters' point is that genetics is more a matter of method of investigation than an explanatory theory. In other words, the application of genetic methods - e.g. artificial mutagenesis, hybridization, linkage mapping - does not count as filling in the gaps of an already established theory but an investigative strategy to learn about diverse biological processes such as development and physiology. In this "investigative pragmatics", gene centric vision is not justified on the ground of a fundamental theory about genotype-phenotype relations such as the metaphor of genetic program suggests. The justification of the gene centric approach is that genetic methods provide new knowledge. Thus, gene centric vision is only pragmatically justified in Waters' account.

On the other hand, the pioneers of genetics, both in the classical genetics and molecular biology, felt a need to ground genetic research on a theoretical ground. Hermann Muller, Francis Crick and Jacques Monod did not see genetics as merely a matter of investigative strategy. Muller (1966) described genetic material as the "initiator and organizing basis of life". Francis Crick (1958) described the set of proteins as the concise phenotype of an organism, the information for which is contained in the genes. F. Jacob and Jacques Monod (1961) described the genetic material as containing the structural information to build proteins as well as a coordinated set of instruction - the genetic program - that determines the developmental and physiological trajectory of an organism.

A preliminary conclusion is that genetics cannot be understood as merely a set of investigative methods. There is, or at least there seems to be, a theory behind genetic research. And this theory-like set of ideas is not a fiction produced by the unity-seeking, theory-loving philosophers of science. It is the product of high calibre geneticists and molecular biologists themselves. These ideas, on the other hand, originate from the interaction from the practice of these geneticists and the ideological milieu of their times. They did not follow from genetics *per se.*

The origin of molecular biology and the origin of computers coincide historically. The origin of molecular biology can be dated to 1940s where the first computers were produced. The first working computer was built in 1946. Shannon's theory of information dates back to 1948, which is the year Norbert Wiener (1948), published his influential book *Cybernetics*. Wiener proposed that the cybernetic ideas were applicable to biological systems such as the nervous system. The key insight was feedback, which enabled an organism to adapt to changing environments.

The computer as an analogue of mind and life has influenced the models of biological functioning. Computers were designed to solve problems, and they relied on their material organization to do so. Organisms also had to solve problems such as producing some proteins when needed, inhibiting some impulsive actions when the need arose and they also relied on material organization. In short, organisms are goal directed systems as much as human artifatcs are. The traditional answer to the goal directed behavior of organisms was to refer to an intelligent supernatural designer. The computer is a material realizer of goal directed behavior and it obviated the necessity for a supernatural designer. This is one of the reasons why biologists, and especially evolutionists such as Ernst Mayr (1961), were so keen to embrace the informational framework.

Ideas flowing from computer science must have influenced the reasoning of biologists. But there was a more direct connection to the work of molecular biologists. For instance, the solution to the problem of inferring 3D structure of macromolecules from crystallography data was made much easier by the use of primitive computers

that used punched cards (Judson 1996). These primitive computers decreased the work load of scientist who would otherwise use pen&paper methods to solve the problem of locating relative distances between atoms of a crystal. The usage of such methods might be important practical determinants for the acceptance of the informational framework.

A point that should be kept in mind, however, is that the informational framework does not fully explain why genetics progressed in the last century or whether it will continue progressing in this century. In other words, progress in genetics was not an extension of the fundamental theory, based on information, into new domains, or filling in the gaps of an established theory. The basic theory, along with its extensions, was adequate in this regard.

The basic theory - that genetic changes cause phenotypic changes and protein sequence is determined by nucleic acid sequence - contributed to the progress by offering a general direction to research. But the "colorful tales" about information and genetic program did not perform such a role - at least not directly.

The idea of coding directed researchers to find out the nucleotide sequences and their effects on protein structure and function. The Mendelian idea that genetic changes cause observable phenotypic changes is another such research orienting idea. The models of population genetics, although they invoked oversimplifications, were useful because they identified ways to construct testable evolutionary hypotheses. That is, population genetics was progressive because it provided a mathematical toolset for modeling evolutionary processes, not because it offered a comprehensive account of the process of evolution from the first common ancestor of organisms to the modern species. Neither did the idea of a genetic program get a hold on biology because it specified the causal pathways from the zygote to the adult organism in a comprehensive manner. It succeeded - besides the historical and sociological reasons - because it promoted the investigation of the mechanisms of gene regulation.

5.4 Conclusion

The progress in genetics came mostly through problem solving practices. The theoretical ideas contributed to the progress to the degree that they offered a general orientation to research.

The investigation based understanding of genetics has advantages over theory based approaches. One such advantage is that, it can explain how geneticists can continue research even if they don't have a comprehensive theory, or when their methods are applicable to a limited domain. Mendelian geneticists continued research even if their theory could not explain the relation between alleles and the respective phenotypes, or the applicability of their analytic methods was limited to discrete character differences - which were exceptions rather than the rule. Molecular biologists could continue research on the genetic code without a hint about actual DNA sequences and with a fragmentary knowledge about the protein synthesis machinery.

If one looks at the evidential basis of these programmes - or paradigms - at the moment of their inception, it is obvious that disconfirming cases are much more numerous than confirming ones. Mendel had based his theory on a single species and a select set of binary characters. His first attempt to extend his theory to a new species resulted in disaster.

What Lakatos said about the early period of research programmes is tailored fit for early Mendelian genetics, the classical period of molecular biology and the founding period of population genetics: they were "submerged in an ocean of anomalies". And these anomalies, at least some of them, were transformed into "corroborating instances" by the successful application of positive heuristics.

The absorption of anomalies is one dimension of scientific progress. The other, more interesting dimension consists of the production of new knowledge. In this aspect, the resolution of difficult problems is very important. In the case of "beaded" trait in Drosophila, Muller and Altenburg not only extended genetic analysis to an apparently

non-Mendelian phenotype but they also discovered the mechanism of balanced lethality.

In the descriptive scheme I gave in the first section of this chapter, I had said that the old problems don't disappear and haunt scientists for a long period. Problems about the role of genes in the determination of traits - i. e. the developmental path between genotypes to phenotypes - is such a recalcitrant problem. The "genetic program" metaphor provided and straightforward but dubious answer to this problem. The genetic program metaphor implies a version of genetic determinism. Genetic determinism will be the topic of the next chapter. The more general methodological issue of gene centrism will be covered in the last chapter in which some of the points only touched in this chapter will be clarified.

CHAPTER 6

GENETIC DETERMINISM

6.1 Introduction

Mendelian genetics had made it possible to trace the inheritance of certain traits across generations. In addition to providing a means to trace inheritance, Mendelian genetics was providing a causal explanation for why some individuals differed from others. Eye color variation in the fruit fly Drosophila, metabolic deficits in the bread mold Neurospora and some human traits such as alkaptonuria could be explained on the same ground: mutations in individual genes were causing the differences in phenotypes. Human behavior was no exception to this form of explanation, at least for some workers in the field.

In 1915, Charles Davenport, an American eugenicist, published a paper on the genetic basis of nomadism, in which he defined the condition as a sex-linked genetic trait.[104] Nomadism in the US was the lifestyle of so called hobos; homeless, unemployed young men who wandered from one state to another by train, making a living by begging, stealing or working in temporary jobs.[105]It was also the common way of life among hired farmworkers who had to move from one place to another, depending on the harvest season of different crops.[106]

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[104] Charles Davenport has many qualifications beyond being an eugenicist, such as being a member of the US Academy of Sciences, the director of Cold Spring Harbor Laboratory. But eugenicist is probably the best term to define his ambitions, and his line of work.

[105] Jack London (2006 [1907]), in his autobiographical work *The Road*, gives a very lively description of this nomadic lifestyle.

[106] According to the US Department of Agriculture, migrant workers constitute only 5% of the total agricultural labor force as of 2007. This number must have been much larger in 1915.

In Davenport's explanatory scheme, nomadism was caused by the inability to inhibit the wandering impulse, and wandering impulse was part of human nature. Nomadism was a sex linked trait because Davenport's data showed two things: males showed this condition ten times more frequently than females and if the mother is nomadic, every child is also nomadic. His data, however was not suitable for building a genetic explanation, because he did not control for the most obvious explanation of inheritance of nomadism from mother to child: the child was totally dependent on her mother and if she lived a nomadic life, the child would follow (Davenport 1915, p. 121).[107] The study, contrary to Davenport's claims, did not also disprove the alternative hypothesis that boys are more prone to nomadism because it was a "more feasible" lifestyle for boys than girls (Ibid. p. 122).

Davenport had transformed a social problem into a biological problem, which would be solved by biological means such as sterilization. In the US, the eugenics program had resulted in confinement of "feebly minded" people in camps or worse, enforced sterilization of those people (Mukherjee 2016). The eugenic vision was carried to its extreme by the Nazis in Germany. Nazis were not only confining or sterilizing those with "genetic" defects, but they ran a program to eradicate them altogether, by euthanasia (Ibid.).

Those dark days are long over. Davenport's (1915) simplistic Mendelian explanation of nomadism now looks as preposterous as astrology or demonic possession. But the tensions surrounding the issue of the genetic determination of human behavioral traits have not disappeared completely. The topic of this chapter is genetic determinism, which is described by Alex Rosenberg as such:

> Genetic determinism promotes morally problematical claim that *socially significant* traits, traits we care about, such as gender roles, violence, mental

[107] The data Davenport gives doesn't even require a statistical analysis to see that there is no genetic influence on the variation between non-wandering vs. wandering individuals. He acts like a religious fundamentalist, who imposes what he wants to see unto the data at hand.

> illness, intelligence, are *fixed* by the genes and not much alterable by environment, learning or other human intervention (Rosenberg 2006, p. 222).

This description perfectly fits with Davenport's (1915) and other eugenicists' vision but in contemporary debates, no one holds such extreme and simplistic beliefs. No scientifically informed thinker believes in the absolute fixity of all behavioral characters and more importantly, the influence of environment in the development of those socially significant traits is conceded by everyone. As Rosenberg (2006) observes, there must be a form of genetic determinism worthy of discussion and the old eugenic vision does not satisfy this condition.

The aim of this chapter is to apply the conceptual tools of genetics in order to answer this question: Can genetic determinism be made a precise, quantitatively formulated thesis? To tackle this question, three concepts would be examined. The first is "the gene for X" where X is a biological trait. This concept is suitable for monogenic disorders but it is not suited to capture more complex conditions such as mental illness or intelligence. The second concept, norm of reaction is good in theory, but it is practically inapplicable to the problems of human genetics because to construct a norm of reaction requires experimenting on humans. The third concept, heritability, is much better than the first two concepts because it does not imply a monogenic perspective, it is a quantitative measure of the overall genetic influence on a trait and its estimation does not require experimentation on humans. However, it is a population specific measure and this casts a doubt on its generalizability. Another problem with heritability is the so called "missing heritability" problem. This last problem is significant because it is an obstacle against the integration of quantitative genetic knowledge with the knowledge gained from recent genomic methods. The upshot of the whole chapter is that genetic determinism as a global thesis is untenable but a more refined framework of the genetic determination of human traits is still worth consideration.

6.2 Gene for X: Two Definitions

In a relatively recent news report on the genetics of bipolar disorder (BD), the title says that "New gene for bipolar disorder discovered" (Universität Bonn 2014). The big news is that, in addition to validating three already known genetic regions associated with BD, two new regions were discovered. But the phrase "a gene for BD" has many connotations beyond the unproblematic claim that these genomic regions are statistically associated with the occurrence of BD. What are these connotations? What is the origin of them and can they survive in the age of genomics? These are the questions to be examined in this section.

One of the connotations of the phrase "X is a gene for Y" (where Y is a phenotypic trait) is the unit character hypothesis. According to the unit character hypothesis, single genes correspond to distinct traits. The organism is a mosaic of traits, each trait being under the control of a single gene. In William Bateson's words:

> In so far as Mendel's law applies, the conclusion is forced upon us that the living organism is a complex of characteristics of which some, at least, are dissociable and are capable of being replicated by others. We thus reach the conception of unit characters which may be rearranged in the formation of reproductive cells.
>
> The organism is a collection of traits. We can pull out the yellowness and plug in greenness, pull out tallness and plug in dwarfness. (Bateson, quoted in Kendler 2005).

Unit character theory, which postulated a one to one relation between genes and phenotypes, didn't survive long. Mendelians, as shown in the first chapter, were not fond of the unit character hypothesis because they were well aware of the complexity of the relations between genes and phenotypes. Neither Morgan, nor Muller or the other inhabitants of the fly lab believed that a single gene can carry the information sufficient in the production of a trait. They saw alternative versions of genes as difference makers. They were the causes of trait *differences* but not the complete

causes of the traits they influence. Genes were units in transmission, not in the production of traits.[108]

Unit character hypothesis was dead even in 1910s, then why beat a dead horse a century later? Preformationism died but its rhetoric survived much longer. In 1976, Richard Dawkins published his influential *The Selfish Gene.* In this popular book, genes were pictured as immortal replicators carried in vessels called individuals. Dawkins was trying to challenge the long held point of view that individuals are the units of selection. His aim was to reconstruct evolutionary history from a gene centered perspective. Although he aimed to deal specifically with evolution, some of his claims and metaphors used to express them went beyond that. He mentioned genes for "altruism, selfishness, alarm calls". Altruism, selfishness, alarm calls are all complex phenotypes. Could they be produced by a single gene? Dawkins knew that they couldn't. Then, what did he really mean?

First of all, the phrases like "the gene for selfishness" did not refer to any observed act of selfishness; it referred to a strategy in the game theoretic sense of the term. In game theory, behavior patterns can be modeled as strategies. A strategy is the set of rules to follow in different situations. The pros and cons of different strategies can be evaluated by simulated matches between two strategies. In an evolutionary game scenario, the success of a strategy against another is determined in multiple rounds. Strategies are allowed to evolve by means of blind mutation and selective retention. Gene for selfishness was nothing more than an acronym for heritable propensity to carry out the selfish strategy.

A common criticism against Dawkins (1976) was that he was promoting genetic determinism. In 1982, he published another book titled *The Extended Phenotype*. In the second chapter of that book, he discussed the difference between gene selectionism and genetic determinism. According to Dawkins (1982), genetic

[108] See the second chapter.

causation is no more "deterministic" than environmental causation. More importantly, Dawkins stated that genetic causes are not *different in kind* from environmental causes. What does causation mean in this context (i.e. biology)?

Dawkins (1982, 11-12) defines causation operationally such that event C is a cause of event R if:

1) C is reliably followed by R (C is statistically associated with R).
2) Experimentally producing C events will lead reliably to R events (i.e. association is validated experimentally).
3) Knowledge of C (i.e. that C happened) will provide a more accurate prediction than the ignorance of it, regarding the question of whether R events will happen or not (i.e. C carries correlational information about R).

Dawkins makes some qualifications to clarify his concept of causation. First of all, reliable association means neither necessity (i.e. R always follows C) nor a strong association (i.e. R follows C most of the time). It just means that the probability of R happening given that C happened is higher than the probability of R happening when C didn't happen, if every other variable is held constant.[109] In the genetic context, this means that having a certain version of a gene raises the probability of having a certain trait, on average.

Secondly, the effects of genetic differences can be overridden or even reversed by environmental intervention and the effects of other genes. Genetic causes are not insulated in the process of development. This point should not be interpreted as implying the inheritance of acquired characters. For Dawkins, environment doesn't change the genes but it can modify their effects. Thus, genetic effects and environmental effects interact in the production of phenotypes.

[109] We might add that if every other variable is allowed to vary randomly, the average raise in the probability of an event will indicate causation.

Dawkins' views on genetic causation, as summarized above, do not promote a problematic form of genetic determinism. But when it comes to defining "a gene for X", his ideas are ambiguous. Dawkins equated "genetic variation for a trait X" with "gene for X" and presented this as an "inevitable", "routine" practice in genetics (1982, 21). This equivocation is a source of confusion. "Genetic variation for X" is synonymous with "gene for X" only if the trait X is Mendelian and this is in conflict with the qualifications he made about genetic causation.

Red eye color in fruit flies and tall vs. dwarf in Mendel's peas are all Mendelian traits in the sense that:

1) There are a few loci with few alleles which influence variation in the traits and their transmission obeys Mendel's laws. In Mendel's experiments, for each character, there were two respective alleles. In Drosophila eye color, there are multiple alleles, but each has a one-to-one relation to the trait variation and each allele was transmitted as a unit.
2) The traits are easily distinguishable morphologically from their alternatives. Mendel's original characters came in dichotomous pairs. The traits studied in early Mendelian genetics were also distinct: there were no intermediate characters.

These criteria conflict with the gradual, probabilistic viewpoint advocated about genetic causation.[110] The definition of "a gene for X" that is implicated by Dawkins' (1982) views on genetic causation can be formulated as follows:

A gene for X is a version of a certain region of the genetic material, which raises the probability of having the trait X in comparison to the alternative versions of that region, *ceteris paribus.*

It is obvious that this differs from a Mendelian trait like *Drosophila* eye color or Mendel's tallness/dwarfness. Each allele that has an effect on the trait variation is

[110] This gradual and probabilistic view of gene effects is similar to Fisher's (1918,1922, 1930) views.

transmitted as a unit, just like any other Mendelian gene: In transmission, every gene is Mendelian. But the trait is not Mendelian because genetic basis of the trait includes many genes with small effect and the total set of those genes are not transmitted as a unit. In this sense, tallness/dwarfness or red/white alleles of Mendelian genetics are totally different from the definition given above.

Dawkins' definition says nothing about the degree of association (i.e. the increase in probability) between the gene and the trait or the size of effects of those genes on the trait variation. To understand the difference, especially in the context of human behavioral variation, we should turn our attention to a more contemporary definition of "a gene for a trait".

Kenneth S. Kendler (2005), a psychiatric geneticist, defines the conditions for the validity of the statement "X is a gene for Y" as follows:

"If X has a strong, specific association with disease Y in all known environments and the physiological pathway from X to Y is well understood, then it may be appropriate to talk of X as a gene for Y" (p.1245).

In the phrase "X is a gene for Y", X is a genetic variant whereas Y is a trait like length, IQ, eye color, schizophrenia etc.[111] We may begin interpreting the conditions sequentially.

The first condition is strong association. The strength of association is similar to the penetrance of a trait but it is a reciprocal relation. High penetrance for a gene implies that the probability of having the trait is high if the gene is present. But a strong association also means that the probability of having the respective gene is also high, given that the trait is present. Mendelian genetic disorders, which are transmitted by individual mutant versions of a gene, conform to this scheme. For complex traits like psychiatric conditions, there are no Mendelian genes in this deterministic sense. It is

[111] The definition is given specifically for disease phenotypes but, as it will be seen later in this chapter, it can be generalized for the genetic basis of any complex phenotype.

possible to have the gene without having the trait and it is also possible to have the trait without having the gene.

A measure of association strength is the odds ratio. Odds ratio is the ratio of the frequency of an event given the condition (e.g. having a gene, being exposed to some risk factor) to the frequency of an event if the condition is not satisfied. For instance, the odds ratio for smoking in relation to lung cancer is 50, which means that the probability of getting lung cancer for smokers is 50 times the probability of nonsmokers. The odds ratio for monogenic disorders is infinite (i.e. X/0). Thus, it is unrealistic to expect such high odds ratios for single genetic variants in multigenic disorders. We might loosen the criterion by comparing the association with the smoking-cancer case. The average odds ratio for the genes found to be associated with psychiatric illness is about 1.3 (Kendler 2005, 1246). Thus, even if we loosen the first condition, it is not satisfied for most variants associated with psychiatric conditions.

The second condition is the condition of specificity. According to this condition, the gene version (X) should specifically influence the respective trait (Y) and nothing else. Let's begin from a counterfactual example. Suppose that a mutation causes blindness. Blindness also inhibits reading, watching TV, understanding facial expressions. Can we say that the gene which is mutated is a gene for understanding facial expressions? Certainly we cannot say such a thing because the mutation does not cause a specific deficit in this capacity.

For a more refined conception, suppose that there is a mutation which causes defective brain development. The individuals with the gene X cannot conceive the emotions reflected by human facial expressions (e.g. fear, happiness, disgust). More specifically, the bearers of the mutant gene X mistake the expression of fear with happiness. Can we say that X is a gene for dreadfulness? It depends on what we deem to be the most prominent effect of the mutation according to our level of psychological knowledge or our social norms.

Let's turn our attention to real cases. In *Drosophila* behavioral genetics, many genes that were discovered to be specifically related to certain behavioral tendencies were found to have other functions as well. For instance, *dunce* mutation was thought to be a gene for associative conditioning, but it turned out to be functional in embryonic patterning and female fertility (Greenspan 2001). Another gene, *latheo,* was thought to be responsible for associative conditioning but it also took part in imaginal disc formation and cell proliferation in the central nervous system (Ibid.). The same is true for the so called genes for geotaxis. Pleiotropy – a gene's functioning in many pathways – is the rule rather than the exception.

More surprisingly, there was no overlap between the genes found to affect wing development discovered by artificial mutagenesis studies and artificial selection experiments (Greenspan 2009). In other words, the intentionally mutated genes which affect a trait are different from those which seem to be associated with the trait after 80 generations of selection (Ibid.). The upshot is that, a similar phenotypic variability can be achieved by changing a non-overlapping set of genes.

In psychiatric genetics, the case is similar except we can't compare artificial mutations with natural variation. A gene variant found to be associated with a specific disease is also associated with other diseases. For instance, serotonin receptor gene variants are associated with schizophrenia as well as bulimia and anorexia. A dopamine receptor variant raises the probability of both schizophrenia and BD.

These facts tell us that genetic changes are not so specific in their effects. This is because genes don’t do anything in isolation and our trait (e.g. disease) categories are not fine grained enough, which brings us to the third criterion proposed by Kendler (2005). This condition is the noncontingency of association between a gene and its phenotypic outcome. The condition is aimed to ensure that, the effect of a gene should not depend crucially on an environmental factor. Let me clarify this point.

Suppose that red hair color is caused by a single mutation. Let the mutant gene be GR and wild type be G. Further suppose that being a redhead makes you

disadvantaged in a society such that redheads are hit in the head in their childhood, they receive less education and food. Consequently, their IQ is very low. Can we say that GR is a gene for dumbness? Or can we say that G is a gene for smartness? Apart from the ambiguity of the trait categories, there seems to be a counterintuitive notion of genetic causation in work here. The initial difference (i.e. red hair color vs. other colors) is genetic, and it can even be a Mendelian trait, but the phenotypic outcome (i.e. IQ) depends on the environment. But if the trait is a Mendelian disorder such that GR specifically causes low IQ *regardless of the environment* one finds herself in, then we might say that GR is a gene for dumbness. But no gene in complex phenotypes has such causally proximate effects on the phenotype.

The causal proximity condition can be understood better if we return back to the lessons of the first chapter. As we saw there, it is safe to call some gene variant a gene for a trait when we know the biochemical steps from the gene product (e.g. enzyme) to the ultimate phenotype. Alkaptonuria and other inborn errors of metabolism were of this sort. The "one gene one enzyme" hypothesis was also proposed in this spirit. The question is whether we have such biochemical knowledge on the etiology of complex phenotypes such as behavior. We are not even near it.

According to the criteria given above, there are no genes for complex and interesting traits. But the Mendelian one to one scheme of representing genotype-phenotype relations is just one of the possible models. There are other means to deal with complex relations between genotypes and phenotypes. One such mean is the norm of reaction.

6.3 Norms of Reaction

Phenotypic properties being fixed by genotypes and their being unmodifiable by environmental intervention are at the core of the debates concerning genetic determinism. But what does it mean for a phenotypical character to be fixed by the genotype?

Let’s begin from the most typical examples: single gene disorders. Cystic Fibrosis (CF) is an autosomal recessive disorder caused by mutations in the CFTR gene. Patients show pancreatic insufficiency, pulmonary infections, sterility and other symptoms with varying intensities (OMIM). It is a single gene disorder but its severity and the comorbidity of symptoms associated with the disease are influenced by at least two other factors, one in the 1st chromosome and one in 19th chromosome Ibid).

When a child inherits two copies of the mutated-dysfunctional copies of the CFTR gene, it is inevitable that the disease will show up at a certain stage of development. There is phenotypic variability in the severity of disease. Some of this variability can be attributed to the variability in the mutations in CFTR. There are nearly 900 different dysfunctional alleles of CFTR (Hartl and Clark 2007, p. 547).

A peculiar character of single gene disorders is, as said above, that they occur whatever the environment one lives in. The severity is influenced for sure by environmental as well as purely stochastic factors but the disease phenotype can't be undone by means of changing the diet or any similar environmental intervention (Kendler 2005). Another peculiarity is that one cannot get the disorder without having the genes. There is no such thing as an environmentally induced CF. There is obviously a linear causal relation here.

A norm of reaction (NOR) represents phenotypic variation as a function of environmental and genetic variables. NORs are usually depicted as two-dimensional figures where the abscissa is some environmental variable of interest and ordinate represents the phenotypic variable. With respect to the concept of norm of reaction, to say that a trait is fully determined by genes is to say that the norm of reaction for that trait is flat (Kitcher 2003, Griffiths 2006). A flat NOR means that modifying the environment has no effect on the phenotype.

Suppose that G1 is the genotype with two defective CFTR alleles and G2 is the genotype with two normal alleles. Let the ordinate represent the level of pancreatic

insufficiency and abscissa represent the level of some environmental variable. To build a NOR, individuals with the genotypes G1 and G2 are raised in a range of environments and their level of pancreatic insufficiency is measured in each environment. The resultant function is the NOR, and if it is flat, the trait is said to be totally under genetic control.

The case so far seems simple enough. But even in the case of single gene Mendelian disorders, matters get complicated when one looks at the details. First of all, phenotypic variability can't be mapped onto genetic variation very neatly. The severity of the CF can't be mapped neatly onto the different mutant versions of the gene. Knowing which of the 900 CFTR alleles (along with knowledge of the alleles at two other locations) a patient has doesn't give precise information for a physician to predict how severe the complications will be.

The central problem with invoking NORs in the debates about genetic determinism is that, there are no NORs for human traits. NORs are acquired by experimental intervention. Individuals are raised in controlled environments. It is impossible to raise human infants in environments of a researcher's choice. The only thing that can be done is to look for statistical associations between certain environmental variables and the variability in the presence/absence or the level of expression of a trait.

Besides, invoking NOR does not solve the actual problems encountered in the search for genetic effects on behavior, contrary to what some scientists and philosophers suggest (Lewontin 1974, Sarkar 1998). NOR had been offered as a model that has a richer information content concerning the causal relations between genotypes, environments and phenotypes (Lewontin 1974). This rich content is obtainable only if many dimensions of the environment are controlled and many genotypes are raised in those environments. In the end, the aim of constructing a NOR is to gain global causal-functional knowledge about the genotype-environment-phenotype relations. Global causal knowledge requires complete NORs: a multidimensional function which incorporates matchings between all possible environments with all possible genotypes. It is theoretically possible to construct multidimensional NORs with prior

knowledge of possible causal factors (Kitcher 1986). This is mainly done by building computer simulations. However, constructing a NOR by experimental methods is much more difficult than building computer simulations.

In experimental practice, a NOR is usually obtained by a much simpler method. NORs are constructed by raising individuals with different genotypes in *two* environments and then connecting the two mean phenotypic values by a straight line (Pigliucci 2001). The slope of this straight line is considered to show the degree of phenotypic plasticity (i.e. environmental modifiability) of the genotype. Although there are multidimensional models for constructing NORs, it would be difficult to interpret the biological meaning of the mathematical function for that NORs and finding a NOR with a "reliable fit" in a multidimensional state space - there are many possible curves that can fit the environment/genotype/phenotype matchings and the NOR is the curve with the best fit - would require a very large data set (Ibid. p. 8). In short, practical constraints force researchers to use simple two dimensional NORs with only two environments, and the phenotypic values in the intermediate environments are filled in with a linear function drawn, without even using regression (Ibid.)

NOR is a useful representation for *visualizing* the functional relations, especially for expository purposes, only if there is a background knowledge about which variables are relevant in the determination of some trait. But it is very suspicious whether NORs would give us a general quantitative framework for functional relations among genes, environments and phenotypes. In order to construct a multidimensional NOR, one should already know a lot about these functional relations. To demand a NOR for deciding whether trait is genetically determined and to what extent, is to put the cart before the horse.[112]

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[112] This is exactly what Lewontin (1974) does. He is correct in pointing to the defects in the linear models used in the estimation of heritabilities. But his proposing NORs as the only alternative causal model promotes pessimism with respect to the discovery of genetic effects on behavior. If NOR is the only alternative to ANOVA and one can't construct NORs for humans, the conclusion is

NORs, in this debate, have been originally invoked against the importance attributed to the results of ANOVA (analysis of variance) studies in human behavioral genetics (Lewontin 1974). In those studies, the core measure of the degree of genetic determination of a trait was heritability. NOR has its problems as I tried to show. Heritability escapes some of those problems - the need for experimentation - but it invokes others.

6.4 Heritability and Genetic Causation

Heritability is a technical concept in quantitative genetics which denotes the proportion of phenotypic variance that can be attributed to variance due to genetic differences. The phrase "due to" is of utmost importance here. Because that phrase means that heritability estimates measure the degree of genetic determination of a trait. In other words, heritability is thought as if it is a measure of *causal influence* of genes in the determination of a trait's value distribution in a population, not just a correlation between phenotypes and genes which will be helpful in predicting offspring phenotypes from parental phenotypes.

As a technical concept, heritability has the clearest meaning in the theoretical framework it occurs in.[113] So, we need to define other key concepts associated with it. Variance is one of them. Variance is a population measure which gives an estimate

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obvious. The overall message of the famous "Analysis of Variance and Analysis of Causes" paper is that behavior genetics is a totally useless enterprise, which I don't agree.

[113]However, this doesn't mean that heritability estimates stay in this safe zone. Nobody would bother with heritability if it was inapplicable beyond the borders of the model fitting practice performed by quantitative geneticists. Heritability estimates are used, efficiently, in animal breeding because narrow heritability, which is defined in the text, determines how much a trait will respond to selection (Sarkar 1998, Falconer 1989). Heritability estimates are also used to determine the degree to which a human behavioral trait (e.g. psychopathologies, personality traits) is controlled by genes. The domain of human behavioral genetics is where the discussion about the merits of heritability estimates is most heated. That is because, heritability in this domain is invoked to argue for the thesis that if some trait is highly heritable, it is more difficult to modify it by environmental intervention, or that individual specific interventions are necessary, rather than changing some widespread environmental condition (e.g. poverty).

of the variation in a population. For any quantitative (i.e. metric) trait like length, a population mean can be measured by simple arithmetic averaging. If every individual's length is "expressed as deviations from the population mean the variance is simply the mean of the squared values" (Falconer 1989, 125).

According to the mainstream quantitative genetics, phenotypic variance (i.e. mean square of deviations from the phenotypic mean= VP) can be partitioned into three components: variance due to genes (VG), variance due to environment (VE) and error variance (e). Thus, ANOVA for a metric trait is expected to give this equation: VP = VG + VE + e. Gene-environment interaction can also explain some proportion of the phenotypic variance. So, an adequate equation will be VP = VG + VE + VGE + e.

VG can further be partitioned into variance due to additive genetic effects (VA), variance due to dominance (VD) and variance due to interaction among genes in different loci (VI).

Broad heritability is the proportion of variance that is due to genetic variation. Whether genes act in an additive fashion or interact with each other is not important in this measure. Thus, broad heritability is VG/VP (=H). Narrow heritability is the measure of phenotypic variance due to additive gene effects. It is given by the formula VA/VP (=h).

Broad heritability is more important than narrow heritability in the debate about genetic determinism because it is said to be "the extent to which individuals' phenotypes are determined by the genotypes" (Falconer 1989, p. 126). Narrow heritability estimates only denote the additive portion of genetic determination. Here, additive means that the contributions of allele substitutions on the total variation in a population are *statistically independent from each other*. As an example, suppose that there are two loci with two alleles which affect the variation in a phenotype (e.g. height) and there is no dominance. Further suppose that the genotypes are AABB, AaBB, AABb, AAbb, AaBb, Aabb and aabb. If the effect of a substitution at the A locus is statistically independent from the effect of substitution at the B locus, the

variance attributable to all such substitutions is said to be additive. Additive genetic variance is the best measure of the inheritance of a character but it is not a complete measure of the genetic determination of a trait. Genetic determinism would be still true even if all of the phenotypic variance can be attributed to gene-gene interaction effects (i.e. VA=0, VI + VD = VP). For instance, if AABB genotypes had a 1.80 m height but all other genotypes were 1.70m - regardless of the environment - all of the variance would be due to the *interaction* of A and B alleles but the trait would still be under genetic control.

Additivity assumption is not confined to the relations between alleles at different loci. A central assumption in the estimation of heritability is that environmental variance and genetic variance can be summed in order to obtain the total phenotypic variance. Supposing that there is an additive relation between genetic variance and environmental variance, and given that we already know the total phenotypic variance, VG and VE can be measured by holding either the environment or the genotype constant and thus, nullifying its contribution to the total variance. One possible way to do this is to standardize environments. But environments include any type of nongenetic influence, thus, it is practically impossible to keep all environmental variables constant (Falconer, Ibid.).

Quantitative geneticists can follow the other road: keep genotypes constant and see how environments influence the phenotypic outcome (Ibid.). This is achieved by using inbred lines, which are thought to be identical in almost every loci. The variance in such a line should solely be environmental. In such a case, VG will be calculated by VG = VP – VE.

The estimation of broad heritability involves conceptual problems. In the equation VP = VG + VE, it is assumed that the environmental component and the genetic component of phenotypic variance are distinct and are in an additive relation. But the environmental sensitivity of every genotype in a heterogeneous population might be different. When estimating heritability in such a population, VG might be overestimated because some genotypes deviate from the mean not solely because of

their genetic properties but also the specific interactions with the environment. In other words, there might be genotype-environment interaction or correlation, which will bias the estimation towards more genetic variance and less environmental variance. The additivity relation is broken if there is significant gene-environment correlation or gene-environment interaction. Before defining these terms, we must examine what additivity means because both GE correlation and interaction are operationally defined as factors that cause deviations from the additivity assumption.

6.5 Additivity and Deviations from It

Additivity in quantitative genetics denotes a quantitative relation between genotypic variation and environmental variation. If there is an additive relation between genotype and phenotype, their contributions to the phenotype are independent of each other. For instance, when genes and environment act additively and the allelic substitution from AA to Aa has -2 phenotypic units (e.g. AA individuals are 2 centimeters taller than Aa individuals) of effect in environment 1, it will have the same effect in environment 2, if there is no gene-environment interaction. The effect of an environmental change will also be constant for each genotype. The case can be represented by parallel NORs.

In the figure below, in the environmental range between E=3 and E=5, there is an additive relation between genotypes and environments. A change from E=3 to E=5 has 2 phenotypic units of effect regardless of the genotype and a change from G1 to G3 (in this region) has 6 units of effect regardless of the environment.[114]

[114] The case of parallelism is important because as I will claim, high heritability implies genetic determinism if and only if NORs are parallel in the range of most actual environments. Extreme environments like E0 in the graph above should be excluded because if we include them in our analysis, we will trivialize the genetic determinism debate. For instance, if E0 represents an environment without any oxygen, no mammals would be able to live there and all phenotypic measurements would be null for every genotype but it would be nonsensical to infer from this fact that genotypes has no effect on the trait of interest.

In this graph, the range between E=2 and E=3 where there is no parallelity and hence, no additivity between genotypes and environments.

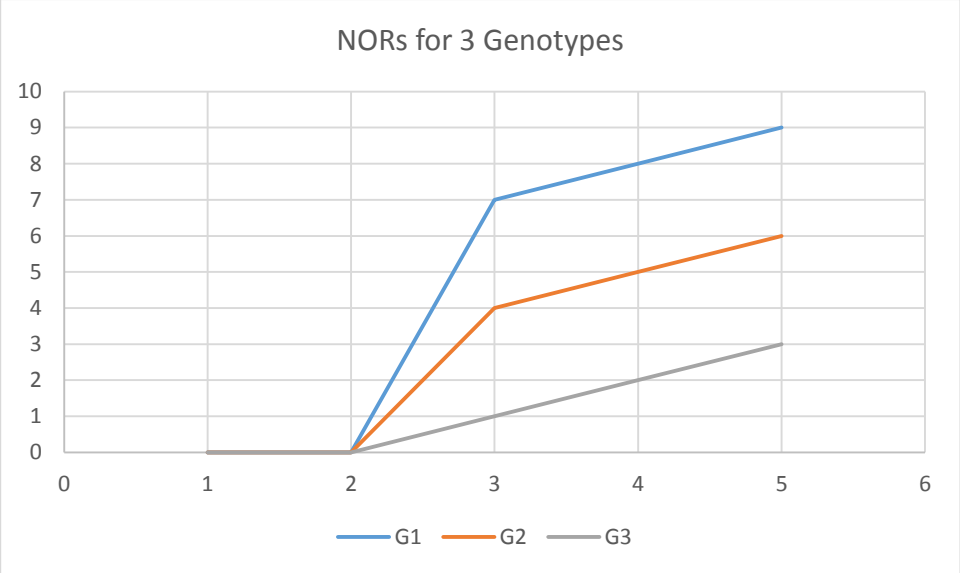

Figure 1. Norms of reaction for 3 genotypes.

Gene-environment correlation is a confounding factor which results from the nonrandom matchings between certain genotypes and certain environments.[115] Suppose that high IQ parents have higher chances to beget high IQ children.[116] High IQ parents also provide an intellectually rich environment to their children. Thus, there is a positive correlation between high IQ genotypes and intellectually rich environments. If this correlation between family environment and genotypes are ignored in the estimation of heritability, the heritability will also include an

[115]According to Falconer (1989), the presence of GE correlation changes the equation to VP=VG+VE+2Cov(G, E). The last term is the term for the covariance of environments and genotypes.

[116] The example is taken from Sesardic (2005).

environmental source of variance: variance due to the differences in family environments. It should be included in the environmental portion of variance because a child's genotype has no influence on the environment she/he will find her/himself in. But there are other cases in which this kind of clear-cut causal distinctions can't be made in favor of the environment.

Neven Sesardic (2005) distinguishes three types of genotype-environment correlations.[117] The first is passive GE correlation. This is the type of correlation we find in the IQ example above. It is passive because the genotypes of children have no power in determining their environments. Reactive GE correlation is such that the correlation is still imposed by the environment but the environment is sensitive to genotypic differences between individuals. Douglas Falconer (1989) states that cows with high milk yield are given more food than cows producing less milk. This creates a positive correlation between milk yield and food consumption. The heritability of milk yield is nearly 0.27, which suggests that there is a genetic component of the differences in milk yields (Hill, Edwards, Ahmed and Thompson 1983).[118] If this is the case, dairy workers' decision to give more food to better cows is partially sensitive to the genetic differences among cows. The environment (husbandry workers) are reacting to a partially genetic difference. Thus, Falconer concludes,

> The covariance, in practice being unknown, is best regarded as part of genetic variance because the nonrandom aspects of the environment are a consequence of the genotypic value and so an individual's environment can be thought as part of its genotype (Ibid. p. 134).

A better example is given by Sesardic (Ibid.). Suppose that children with higher IQ are given more intellectually demanding tasks than children with lower IQ. Also

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[117] See also Plomin, Defries, McCLearn, McGuffin (2008, pp. 318-325) for a similar classification and the methods for detecting the three types of genotype-environment correlation.

[118] These heritability estimates are population specific and their range of values in high confidence intervals range widely. For instance, in the study cited, estimated heritabilities differed between 0.24 – 0.36. An interesting result of the study was that high yield strain had a higher heritability. There are more dramatic cases in which the heritability of a trait (e.g. IQ) ranges from 0.29 to 0.73 in the 95% confidence interval in only one study(Gilbert 2002, p. 131).

suppose that dealing with more demanding tasks improves one's IQ. If IQ is heritable – IQ differences reflect some genetic differences – then it can be said that the society is selectively responding to a genetic difference which results in an increase in the difference. The narrow heritability of IQ, which is estimated from twin and adoption studies, is nearly 0.5 (Plomin, Defries, McCLearn, McGuffin 2008, p. 162). So, nearly half of the variation of IQ can be attributed to genetic differences. According to Sesardic (2005), most behavior geneticists would not include the variance due to GE correlation in VG or VA because it would violate some intuitive ideas about partitioning causes (p. 94). Society is the active-agentive cause here, so it would be intuitively false to consider its selective actions as genetic causes. Let me explicate the last point with a thought experiment borrowed (and adapted) from Richard Dawkins (1982).

Suppose that enjoying cooking is a phenotype only observed in females and the difference between being a male or female is 100% heritable because it only depends on the sex chromosomes one has got. Also suppose that society trains female children to cook and male children not to cook. Would you call the difference between enjoying cooking or not enjoying cooking a phenotypic difference *caused* by genetic differences? If you only trace heritabilities, it would look as if it is wholly genetic. In Dawkins' (1982) understanding of causation (i.e. causation=correlation=prediction), the case would be a perfect case of genetic causation. But a more commonsense interpretation would lead to the conclusion that society is the locus of causation here. This doesn't mean that society has a control over the genetic property of being male or female. This only means that the correlation between sexes and the trait of enjoying cooking is arbitrarily imposed by the society, without any prior genetic mediation (i.e. females are genetically more prone to enjoying cooking). Sesardic's (2005) claim about the attitude of behavioral geneticists makes sense in this context: No genetic mediation of environmental influence, no genetic causation.

More interesting cases lie in between arbitrary (i.e. independent of genotype) environmental influences and the interaction of genetic predispositions with the

environments. Active GE correlations, along with GE interactions, provide such interesting cases.

Active GE correlation occurs when individuals with different genotypes actively select or create their environments and their choices causally depend on their genotypes (Plomin, Defries, McCLearn, McGuffin 2008, p. 318). Suppose that before the domestication of dogs, some wolves with a peculiar genotype tended to approach human settlements and began feeding on human wastes. Further suppose that the genetic changes related to this type of behavior also reduced these breed of wolves' hunting frequency and aggression towards humans. In addition to selecting their environments (i.e. preferring to wander around human settlements), imagine that the playful behavior of these protodogs change the behavior of humans against dogs. Playful behavior in the protodogs' side created a friendly response from humans, which propagated into other human settlements through cultural transmission and resulted in the culturally transmitted dictum "some wolves (protodogs) are the best friends of humans". This, in turn created customs for taming dogs by special techniques. In this scenario, the behavioral difference between wild and pro-domestic wolves is mostly due to genetic differences, even if there is a taming effect of wolf-human interactions. Because taming itself came as a response to the genetically caused playful behavior. Protodogs and wild wolves differed genotypically, this difference resulted in different preferences of environments and protodogs' genetically different behavior even changed their environment (i.e. the dog friendly human settlements) which resulted in further behavioral differentiation between wild wolves and protodogs through taming.

Gene-environment interaction denotes the differential sensitivities of different genotypes to environments (Falconer 1989, Plomin, Defries, McCLearn, McGuffin 2008). In the example above, protodogs and wild wolves had different sensitivities to taming. For the sake of conceptual clarity, let's think of the most radical imaginary case: G1 (=genotype 1) people have an average IQ of 120 when raised in Çankaya

and they have 80 IQ when raised in Mamak. G2 people show opposite results (i.e. 120 IQ in Mamak and 80 IQ in Çankaya). We would get a NOR like this:

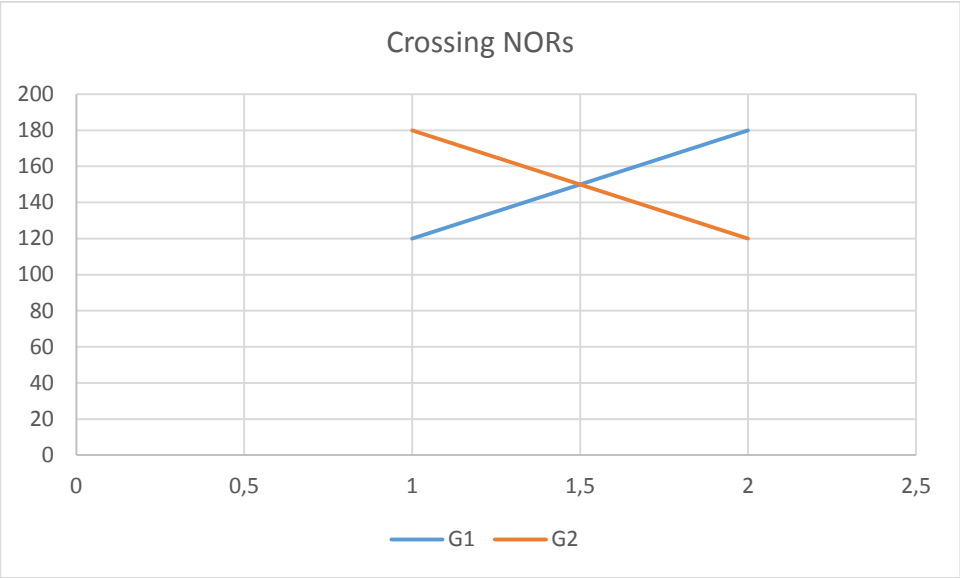

Figure 2. Crossing NORs. See text for explanation.

The NOR above suggests that there is no main effect for genes or the environment. In other words, neither genes nor environments have distinct effects. The only thing that determines the distribution of phenotypic values is the interaction between them. This would amount to the following equation: VP=VGE. It is impossible to partition the variance; hence, we might say that the concept of heritability loses its meaning in such a case (i.e. crossing NORs).[119]

[119] Sesardic (2005) claims that heritability doesn't become meaningless in this type of cases but it just takes the value 0. This suggestion would be correct if heritability had been a variable like electromagnetic field. Even a zero value for electromagnetic field can answer some meaningful questions : Why doesn't this charged particle accelerate? Zero electromagnetic field is still explanatory because the electromagnetic field is a vector field, which consists of forces. Heritability, in contrast, is a dimensionless parameter. Zero heritability due to crossing NORs doesn't even mean that genes have no effect on the phenotype, or that genes have an effect but it is counterbalanced by

The crossing NORs *with no mean effect* should be the exception rather than the rule. But even a less dramatic deviation from the additivity assumption sheds a cloud of doubt around the causal interpretation of heritability.

Heritability, in its technical domain, is said to be a measure of variance *due to* genetic variation. Variance itself is a measure of phenotypic variation. Thus, heritability is originally an *indirect* estimate of how much nature (i.e. genes) *determines* the phenotypic differences between individuals. Heritability is expected, at the least, to give an indirect but reliable causal knowledge about the genetic sources of phenotypic variation. The fact that heritability of a trait depends on the specific allele distribution in a population and its environment casts doubts on its usefulness in providing information about the causes of phenotypic variation. Causal knowledge should be general, if not universal, and a context dependent measure can be misleading in inferring causal connections. Let me clarify this point a little bit more.

Heritability is measured in a specific population. This means that, a population with a specific distribution of genotypes and which is maintained in a specific environmental range is being examined. So, both the environmental and genetic variability of the sample population is constrained. For this reason, the causal knowledge gained from the estimation of heritability will have serious constraints in its generalizability.

According to Lewontin (1974), heritability is a local value. It is valid only for a certain population at a certain time. This means that, heritability of a trait can change from population to population. The mathematical formula for heritability - VG/VG+VP - implies two limiting cases: 1) If the environment is equalized for every

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the environment. It just means that VP cannot be partitioned into VG and VE. But if heritability had been null because VE=VP (e.g. religious preferences have zero heritability), then all of the NORs would overlap with an identical slope (i.e. VP≠0) and VG=0 would still be meaningful. Because in this case, we *intuitively* know that the environment is the *driving force*. This knowledge does not come from the heritability estimate itself but from our background knowledge about how people are indoctrinated in the course of becoming a believer. The crossing NOR case is so counterintuitive that an analysis of causes becomes meaningless.

individual in a population, VE will be zero and heritability will be 1. 2) If genotypes are equalized, then, heritability will be zero.

A more realistic - but still hypothetical - scenario for the variability in heritability is given by Flint, Greenspan and Kendler (2010). In this scenario, in an isolated European population, the heritability of schizophrenia is estimated to be 0.7. Then, a virus epidemic begins and the infection seriously increases the risk for schizophrenia. Heritability is estimated again and it is found to be 0.5. Afterwards, immigrants with different genotypes enter this population. Some of them carry schizophrenia risk genes. So, they contribute to genetic variance for schizophrenia and heritability increases to 0.8. We can conclude from this scenario that heritability estimates are – by definition – sensitive to population parameters such as the genetic constitution of the population and the environment the population lives in.

One problem with locality – being dependent on population parameters – is that it constrains the generalizability of heritabilities across populations. Another related problem is that heritabilities become misleading in the search for causal knowledge. Heritability in the broad sense is said to be a measure of the genetic influence on the distribution of a trait. In other words, heritability is introduced as the measure of the effect of *nature* in opposition to *nurture*. If heritability is itself dependent on the environment, how can we say that genetic variation is causing the variability of a phenotype?

The NOR perspective offers a nice illustration of this point. Consider the hypothetical scenario given by Sarkar (1998, p. 83).In the environmental range e1, the heritability is nearly 1. But the trait shows considerable environmental variability. Compare e1 with e2. In e2, variation is completely genetic. If we have estimated heritabilities in both ranges, we would acquire similar results. But the effect of environment in e1 on the variability of the trait is significantly higher. Would we still say that nature is

more important than nurture in e1, given that heritability is nearly 1?[120] According to Lewontin (1974) and Sarkar (1998), this is a case which shows that heritability of a trait (low or high) says no interesting things about the causal relations that explain the genesis and the variation of that trait. They don't say that there is no such thing as genetic determination; they just claim that heritability does not give causal-functional information. In Sarkar's (1998, p. 90) words:

> A high value of H (or h) does not necessarily indicate a strong influence of natural factors (where those are being interpreted as genetic ones). Conversely, a low value of H (or h) does not indicate a strong influence of environmental ones.

Can we conclude that heritabilities are useless in every condition? No. They are useful, or more correctly, they lead to useful generalizations, only if the additivity relation is not broken frequently. In other words, if the NORs are approximately parallel in a sufficiently inclusive actual environmental range, heritability measures provide a coarse but useful picture of the relations between genotypes, environments and phenotypes.[121] Whether most NORs are parallel, i.e. there is no variation in phenotypic plasticity (Pigliucci 2001) in the actual range, is an empirical question still not answered conclusively (Sesardic 2005). This lack of evidence, that would settle the debate once and for all, calls for a case by case evaluation.

Behavior geneticists and quantitative geneticists are well aware of the limitations of heritability estimates, especially those obtained in humans by twin or adoption designs (Plomin et al. 2008, 85-90; Falconer 1989; Holland, Nyquist, Cervantes-Martinez 2003; Flint, Greenspan and Kendler 2010). So, why are they still attached so strongly to the concept and the methodology? Is this really an "obsession"

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[120] In fact, we might say that the population in range e1 is a different population from the one in e2. Populations can't be defined solely by means of their genetic constitution. If these points are accepted, Sarkar and Lewontin's claim boils down to the trivial fact that heritability is not a measure designed to compare two different populations.

[121] They give a coarse picture because just like biometrical models discussed in the second chapter, quantitative genetic models of metric characters usually ignore the causal-mechanical details that produce those statistical patterns obtained in the ANOVA experiments.

motivated by a political agenda, as Sarkar (1998) suggests?[122]The reason, I think, is mostly pragmatic.

For the quantitative geneticists, the preference to use the methodology of ANOVA is plainly opportunistic. Quantitative geneticists usually work on improving the efficiency of artificial selection in farm animals or plants. Narrow heritability is a reliable measure of the response to selection. In other words, heritability is a reliable measure of the efficiency when artificially selecting for an economically valuable trait such as milk yield.

Quantitative geneticists are well aware that heritabilities change between environments but this provides an opportunity rather than a disadvantage. If a trait of interest is more heritable in one environment, then perform the artificial selection exactly in that environment. As we saw in the second chapter, Fisher suggested recourse to statistical methods when it is impossible to construct a Mendelian analysis of the causal underpinnings of phenotypic differences. This opportunistic spirit seems to be shared among the practical workers in the field.

Behavior geneticists have one commonly expressed reason to continue using heritability estimates: a high heritability (e.g. 0.5) shows that there is considerable genetic influence on the trait considered. In other words, heritability estimates show a researcher where to begin digging (Sesardic 2005, 24). Plomin et al. (2008) express this viewpoint, along with optimism about the new opportunities created by the genomic era:

> Estimating whether and how much genetics influences behavior is an important first step in understanding the origins of individual differences. But these are only first steps…. Moreover, the behavioral sciences are at the dawn of a new area in which molecular genetics will revolutionize genetic research by identifying specific genes responsible for the heritability of

[122] Sarkar (Ibid. 92) expresses his suspicion of a political agenda specifically for behavioral geneticists, not quantitative geneticists in general. I believe that the myopic vision of behavior geneticists is more like an occupational disease rather than the expression of a latent conservative ideological position.

> behavioral traits. Identifying genes will make it possible to address multivariate, developmental and gene-environment interface issues with much greater precision. It will also facilitate the ultimate understanding of the pathways between genes and behavior. (p.90)

This means that *the estimation of heritability is just the beginning of a more through genetic investigation* (Sesardic 2005, p. 25). We are told that the genetic mechanisms that produce behavior will be uncovered by using the techniques developed in molecular genetics. The problem with this promise is that there is no straightforward way to integrate the findings of quantitative genetic methods such as twin and adoption studies and genomic methods such as genome wide association studies. The so-called missing heritability problem is a nice example that demonstrates the difficulty in a smooth integration between traditional behavior genetics and genomics. However, it is also not a complete refutation of the research program which searches for the genetic underpinnings of behavioral variation.

6.6 The Missing Heritability Problem

Heritability in the broad sense - the total genetic portion of phenotypic variance including additive, dominance and epistatic effects - is more important in the general philosophical controversies on nature vs. nurture. In human behavior genetics, as well as other areas of quantitative genetics, heritability in the narrow sense (=h) is more important than broad sense heritability because only h gives an estimate of the parent-offspring correlation (Visscher, Hill, Wray 2008). This results from the fact that humans and other subjects of quantitative genetic investigations are usually diploid organisms in which segregation allows the transmission of only one allele from each parent. Thus, dominance variance (VD) is not transmitted (i.e. only one allele in the locus is transmitted, which prevents intra-loci interaction effects from being transmitted). Epistatic or interaction variance (VI) is not transmitted for similar reasons. Along with the fact that h is a straightforward measure of response to selection (response to selection equals narrow sense heritability times the selection coefficient, Ibid.), it is reasonable to concentrate on narrow sense heritability, even if the philosophical discussion revolves around broad sense heritability.

The heritabilities of milk yield and IQ I gave in the last section were all narrow sense heritabilities. Narrow sense heritability, by definition, has to be lower than broad sense heritability. Even with these lower heritabilities, we encounter a serious discrepancy with the heritabilities measured by molecular genetic methods and the results obtained from older quantitative genetic methods - i.e. twin and adoption studies.

The missing heritability problem can be summarized like this: When we use twin or adoption designs (or a combination of both) to calculate heritabilities of human psychological traits such as psychopathologies or dimensions of personality, we obtain fairly high values: 0.5 on average and higher for some psychopathological conditions such as schizophrenia (Plomin et al. 2008). But when we use the most up to date genomic method - genome wide association studies - to detect the genetic bases of the variation in those traits, variation in the discovered DNA regions can explain only a small proportion of the phenotypic variance, as little as 5 percent.[123] So, some part of the heritability is missing in the sense that it can't be located in the genome by means of genome wide association studies.[124]

In 1990s, association studies successfully identified quantitative trait loci (QTL) in experimental organisms such as house mouse *Mus musculus* and *Drosophila melanogaster* (Flint and Mackay, 2009).[125] In this research, it was shown that

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[123] Missing heritability has become an issue in medical genetics, rather than behavioral genetics. The traits in behavioral genetics (e.g. dimensions of personality) share a common property with common diseases like atherosclerosis or diabetes: they are complex. Complexity of a phenotype doesn't have an objective definition, it only means that there are multiple genes that influence the phenotype.

[124] Missing heritability might mean two things: the heritabilities obtained by statistical methods are real but they just can't be detected by the methods of molecular genetics. In this case, it is better to call the problem "the hidden heritability problem". It is also possible that the heritability estimates provided by quantitative genetic methods themselves are dubious.

[125] A QTL is a region of a chromosome whose variation is thought to contribute to the variation in a quantitative trait. QTLs are identified structurally by means of markers. As you might remember from the first chapter, in Mendelian genetics, markers are genomic regions which have two properties: their locations are known and they have easily detectable phenotypic effects. In the genomics era, it is not necessary to use markers with easily detectable phenotypic effects. The positions of markers can directly be known from genotyping or DNA sequencing, without any prior

quantitative traits are influenced by a few QTLs with large effects. For instance, substitution in a single QTL could explain 10% of the difference between two experimental populations. It was found that top 6 QTLs could explain 84% of genetic variation (Miles and Wayne 2008).

Early association studies as the ones above were performed in small samples. When the same studies were conducted in larger samples, it was discovered that there were many more QTLs with smaller effects and more importantly, the effect sizes discovered beforehand were exaggerated (Ibid). These results gave support to a model with few genes of high effect and many genes with small effects. This type of genetic architecture might be called the exponential architecture because there is an exponential distribution of effects sizes and number of genes involved (Flint and Mackay 2009).[126]

Given the exponential model, the expectation in human medical genomics was to find those high effect variants. If a marker is tightly associated with a large increase or decrease in a quantitative trait, it is reasonable to search for the genes responsible for the change, in the vicinity of that marker. These genes are candidate genes. There were initial successes such as the case of the epsilon 4 apolipoprotein (*APO*E4*) variant in late onset Alzheimer's disease (Ibid.) but as more and more linkage studies are conducted, many candidate genes were rejected because the results of earlier studies could not be replicated.

A problem with former QTL studies was that the number of markers used as well as sample sizes were low. This led to low resolution in mapping and low statistical

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knowledge of their effects. In fact, it is better to have molecular markers because markers with observable phenotypic effects can interfere with the investigated trait via pleiotropy.

[126] Compare this with Morgan's model of gene action discussed in the second chapter. I had called it the spectrum view of differential specificity. The difference between two outlooks is that the first is about the genetic architecture of a single phenotype whereas the second is about genotype-phenotype mapping function in general. The first concerns the many to one relations between certain genes and a complex phenotype but the second also involves many to many relations, and thus, pleiotropy.

power. For instance, a QTL tags a genomic region of tens of centimorgans. There may be many genes and regulatory regions in such a large genomic portion. GWA studies were introduced in 2000s as a high resolution, as well as hypothesis free method for detecting the genetic basis of complex traits such as body mass index or schizophrenia. The high resolution of GWA studies is a result of using hundreds of thousands of single nucleotide polymorphisms (SNP) at once.[127] GWA is hypothesis free in the sense that it doesn't depend on prior knowledge of genomic locations (i.e. a knowledge of the sites that probably contain causal or risk variants) (Visscher, Brown, McCarty and Yang 2012).

Genome wide association studies (GWAS) aim to discover disease associated single nucleotide polymorphisms (SNP) by comparing the differential distribution of these SNPs in the genomes of case (i.e. those having the disease) and control groups. The SNPs found to be associated need not indicate protein coding regions. They may be on regulatory genetic regions or noncoding DNA. But once a SNP with significant association is found, its position gives researchers where to look for candidate genes.[128]This is because the SNP found is expected to show linkage with a nearby gene (i.e. linkage disequilibrium).

The narrow sense heritability obtained by the classical methods of quantitative genetics (i.e. twin and adoption studies) of Schizophrenia is 0.7-0.8 (Wray et al. 2013, p. 508). In a recent GWA study (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014), 108 genomic regions have been found to be significantly associated with the condition. These 108 variant could explain only 7% of the phenotypic variation (Ibid. p. 424). What is happening here?

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[127] Single nucleotide polymorphisms are a class of genetic variants which involve the change in only one nucleotide in a certain position in the genome. For instance, a certain position on the 4th chromosome might have the nucleotide adenine whereas in some people, the nucleotide is guanine.
[128] A candidate gene is a gene that is considered to be important in the *etiology* of a phenotype (e.g. a disease).

A part of the problem is that significance thresholds in GWAS are too low. In a GWA style study, many variables are assessed at once, with respect to their effect on the distribution of some measurement - e.g. a disease. For each variable - in this case, SNPs are the variables - a test is carried out to find out whether its association with the disease is random or not. Since hundreds of thousands of SNPs are tested at once, there would be false positives - SNPs associated randomly with the trait but which in reality have no effect - and false negatives - SNPs that affect the trait but association is not found. To eliminate false positives, p values are lowered below a certain threshold value. This significance threshold value depends on the number of tests - number of SNPs - carried out as well as the genetic structure of the populations examined (e.g. linkage disequilibrium). The upshot is that, the statistical methods used to avoid false positives prevent researchers from including low effect SNPs. False positives are eliminated at the cost of raising the false negative rate.

In Fisher's infinitesimal model discussed in the second chapter, quantitative (i.e. continuous or metric) traits were deemed to be influenced by indefinitely many genes with infinitesimal effects for each. Significance of association can be lowered if the gene variant linked to the SNP has a very small effect on the phenotype. Small effects don't automatically lead to higher P values (i.e. weak association). This is because, if the small effect is robust - it is independent of the genetic background and the environment - it will eventually show up in large samples. But usually, small mean effects can easily be swept by countering effects from either the environment or the genotypic background. This is why small effects of gene variants are as troublesome as ambiguous effects of gene variants. A gene variant has an ambiguous effect if it makes a contribution to the trait variation in one direction in some context (i.e. genotype and environment) but a contribution in the opposite direction in another context. Ambiguity and small effects are two sides of a coin.

Another limitation is that GWA studies are made in case and control groups. A case vs. control design imposes an artificial structure onto the actual variation in a population. It represents the population as if there are individuals unambiguously

having the trait and those which do not. But according to the infinitesimal model, even if the diseased vs. healthy division is a discrete one, liability to disease must be normally distributed in the population (Plomin, Haworth and Davis 2009). An implication of this assumption is that, disease condition lies in one extreme of this distribution whereas controls are selected across a wider spectrum in the normal distribution. An overlap in susceptibility alleles in cases and controls might lower the strength of association between certain variants and the disease. If a SNP is found in both cases and controls and its effect is small, it will not be detected by GWAS. The strength of association between a single SNP might be small, but susceptibility variants may form networks that are functional in the determination of some deeper phenotype (endophenotype) than the disease: "For example, five SNPs associated with coronary heart disease all seem to be involved in intracellular vesicle trafficking" (Ibid., p. 876). Other endophenotypes might include fasting glucose levels for diabetes, blood LDL levels for coronary artery disease or prepulse inhibition in schizophrenia.[129]

If the infinitesimal model and the network hypothesis are correct for complex phenotypes, it is safe to include genetic variants with lower-than-threshold P values in the calculation of GWAS derived heritabilities.[130] When the additive contributions of these hundreds of SNPs are taken into account, heritabilities explained by these SNPs will increase. For instance, nearly 50 SNPs had been discovered to be

[129] It is dubious whether endophenotypes have a simpler genetic architecture with a small number of high effect variants (Munafo and Flint 2014).

[130] The aim of GWAS is not the estimation of heritabilities. In fact, the acceptance of this theoretical outlook (i.e. infinitesimal plus network approach) achieves much more than solving the so called missing heritability problem. GWAS were originally performed with the common disease common variant approach in mind. According to this approach, susceptibility to common diseases (>0.01) depend on a modest number of common gene variants with modest phenotypic effects (Gibson 2012). It is very similar to the candidate gene approach in which a small number of common and high effect variants are searched for. What GWAS could detect so far has been much different from these models: a small number of modest effect variants and many variants with very small effects. The infinitesimal plus network approach will provide a new target: candidate networks rather than candidate genes. This might be the real revolution brought out by GWAS and data mining techniques – that identify networks – combined.

significantly associated with human height but these explained only 5% of the variance (Yang et al. 2010). When the totality of common SNPs (nearly 295k) was taken into account, 45% of the heritability was explained (Ibid.). However, including all SNPs seems to make the whole GWAS enterprise meaningless because the aim of GWAS is not to account for heritabilities but to find the genetic basis of disease and other phenotypes. To do that, one might be able to *dissect the specific portions of genotype that are associated with the phenotype*.

Increasing the number of SNPs by decreasing significance thresholds is one way to solve the missing heritability problem. Another way is to look for gene-gene interactions. Quantitative genetic methods of heritability estimation are usually insensitive to the effects of epistatic interactions. Epistatic interaction component of variance, VI, might be inadvertently included in the additive component VA. Missing heritability might be missing not because enough variants aren't discovered but because the narrow sense heritability has been overrepresented in the first place (Zuk et al. 2012).

An alternative possibility is that rare alleles with large effect sizes will explain most of the heritability. In GWA studies, SNPs that are common in the population are used as markers. However, it might be the case that there are rare genetic variants, such as copy number variants, which have large effects on the prevalence of disease. For example, in schizophrenia, very rare genetic deficits (e.g. a microdeletion or microduplication, only seen in one person) with large effects are shown to be associated with the disease (Walsh et al. 2008). A similar case may be true for autism (Bendesky and Bargman 2011). Since these genetic deficits are very rare, they can't be detected by GWAS which searches for common SNPs.

There are two interrelated issues in finding the genes associated with certain traits: the genetic architecture - which is also called the genetic basis - of a trait and the frequency distribution of alleles that influence a trait. Genetic architecture denotes the number, the distribution of effect sizes - e.g. exponential vs. infinitesimal - and interactions of the gene variants involved in the variation for a trait. Missing

heritability might be explained by the complexity of the genetic basis (e.g. infinitesimal model) or by the allele frequencies. If heritability is missing because diseases are caused by many common variants with very small effects, decreasing the significance threshold and increasing the sample size would be the solution. If the problem is caused by the weakness of GWA studies in detecting large effect rare variants, then the solution would involve more through genotyping methods specifically designed for detecting such rare variants.

Either way, GWA studies have shown so far that finding the genetic bases of complex phenotypes is very difficult. Some of this difficulty is attributable to the complexity of genetic architecture itself and some of this can be attributed to the genetic heterogeneity of human populations. How could these points translate into the debate concerning genetic determinism?

6.7 Missing Heritability and Genetic Determination

The phrase "genetic determinism" loses much of its significance within the new conceptual framework of genetics. The prototypical examples of genetic determinism, as exemplified by Davenport (1915) and monogenic disorders, involved a few genes with fairly strong, direct links to the phenotype.[131] The findings of new forms of genetic analysis such as GWA cannot be interpreted in those simple models. So, from now on, the focus will be on the genetic determination of traits, not on an unclearly defined theoretical position with no follower. Accordingly, we might reformulate the question asked in the previous section like this: How could polygenic inheritance and genetic heterogeneity be translated into the debates concerning the genetic determination of traits?

Complexity - i.e. polygenicity - of the genetic basis of a trait, or the heterogeneity of the genetic causes of a trait should not be used as arguments against genetic

[131] In Davenport's (1915) case, the association was imaginary; in monogenic disorders, it is real.

determination without caution.[132] Think of two cases. In the first case, the trait is influenced by a few genes of major effect. The heritability is high and it can be explained exhaustively by these genes. We can safely say that the trait is genetically determined.

In the second case, the heritability of a trait is 0.9 and its genetic basis consists of 1000 loci with very small additive effects. Suppose that the trait is height and total variance in the population is 20 cm. 18 cm of this variance is explained by the variation in those loci. If the loci have equal effects, a single locus will contribute 0.018 cm to the phenotype. Every single gene has a very small contribution but their aggregate effect is very high. It is safe to say that the trait in question, in the specific population and the specific environment, is genetically determined. In short, the number of genes might be large but genetic determination might still be correct for a trait. Many-to-one relation between genes and a trait just makes "gene for X" concept obsolete, as I have shown in the first section.

A similar conclusion is true for the genetic heterogeneity of certain traits such as autism. Suppose, as Bendesky and Bargman suggested (2011), that autism is not a common disorder but a collection of rare genetic disorders. In other words, every subgroup of this collection has a common genetic defect not shared by the other subgroups. But the disorder is still genetically determined, because it is assumed to be caused by a genetic deficit. One might say that Autism Type 1 is caused by the rare variant 1; Autism Type 2 is caused by rare variant type 2, so and so forth. Rare variants, just like small-effect common variants, only refute a very simple form of genetic determination. A more refined form of genetic determination, which allows for genetic heterogeneity and polygenic inheritance is still defensible. In short, many to one relations between genes and phenotypes - e.g. many genes influencing the same trait or different gene combinations producing the same trait value - does not

[132] Rosenberg (2006, p. 35) falls into this error when he says that the heterogeneity at the genetic basis of some traits refutes genetic determinism.

refute genetic determination. The only thing that can refute genetic determination is *one to many* relations between genotypes and phenotypes: the same genotype leading to many different phenotypic outcomes in different individuals, either by means of the environment or in a purely stochastic fashion.

Then, one might wonder, what does the missing heritability problem tell us, beyond the trivial conclusion that complex traits are not similar to monogenic disorders? First of all, genetic architectures of different complex traits might be different. Some traits like IQ or height might fit better to infinitesimal models whereas susceptibility to infectious diseases or drug responses might depend solely on large effect variants (Eichler et al. 2010, Bush and Moore 2012). If this is the case, there would be no single solution to the problem of missing heritability. A trait based approach would be better.

Missing heritability problem should not be interpreted as a straightforward refutation of the findings of quantitative genetics. The quantitative genetic methods have led to successes in identifying the gene-trait relations in model organisms and successes in selective breeding in domesticated organisms. Heritabilities estimated from pedigree studies conform to selection responses in animal breeding research, which shows that the older quantitative methods have estimated heritabilities correctly (Manolio et al. 2009). Heritability estimates obtained from twin and adoption studies in humans have proved to be robust and replicable (Plomin et al. 2008). The difficulty lies not in the numbers but in their causal interpretation. Which genes influence the trait of interest and by which mechanisms were the questions for which GWA studies were expected to give clues.

Some commentators in the early days of GWAS have suggested that it has not satisfied the expectations.[133] What were those expectations? The simplest expectation

[133] Visscher et al's 2012 review has a very nice section which reflects the common opinion of scientists and science reporters. The common conclusion is that GWA studies have not found causal variants for disease or other complex phenotypes.

was to find common (frequency > 0.05) variants with large and additive effects. This common disease - common variant hypothesis turned out to be wrong. The detection of a gene variant in a GWA study depends on two things: the minor allele frequency and the odds ratio (Manolio et al 2009, 749). Minor allele frequency is the frequency of the rarer SNP in a certain genomic location. Odds ratio, as told above, is a measure of the probabilistic effect size of a variant on the value of a trait. So, the success of a GWA study in identifying genetic variants depends on the effect sizes and population frequencies. These provide technical limitations which can be overcome by using bigger samples or more SNPs, or other genetic variants such as copy number variants. Even under these limitations, GWA studies have identified much more replicable associations than the old methods such as linkage analysis (Munafo and Flint 2014). This success being a fact, there is still a great gap between identifying gene variants that are associated with a trait and constructing a causal story about how those variants affect the trait. Follow-up studies would show the validity of GWAS findings and how they would be integrated into a more comprehensive causal understanding about the etiology of disease and other phenotypes.

6.8 A Subtle Form of Genetic Determinism

So far, I've tried to give a precise description of genetic determinism by using three concepts: the gene for X, norm of reaction and heritability. None could give a clear-cut description of genetic determinism which is defended by the so called genetic determinists. This is because, as we move away from the rhetorical jungle of vulgar discussions and approach what the scientists are actually saying, defining a position in simple terms becomes impossible. For instance, nobody can charge the so called genetic determinists for defending a monogenic perspective in human behavior. Neither is heritability a perfect ground for defining genetic determinism. A heritability above 0.5 cannot justify the thesis that the trait in question is more a matter of genes than the environment, because heritability constrains the effects of environmental intervention only in the range of environmental variation already

inherent in a specific population (Sesardic 2005, p. 154).[134] An intervention beyond that range changes the situation. The discovery of a new method of intervention cannot be constrained by heritabilities.

Now, I want to introduce a different take on the same issue offered by Jonathan M. Kaplan (2000). I will revise some of his ideas in order to uncover what scientists really think when they say that genes are very important in determining the phenotype of an organism.

Jonathan Kaplan (2000) identifies three different forms of genetic determinism. According to the first one, the genome of an organism carries the complete information for specifying the properties of an individual. Kaplan states that this view has no contemporary defendant. A viewpoint similar to this one has been defended by Walter Gilbert (1992). But there is major difference between Gilbert's view and the first form of genetic determinism offered by Kaplan. According to Kaplan's definition, the genome determines the total set of the phenotypic properties of an individual. In Gilbert's vision, on the other hand, the genome totally specifies the species-typical properties of an individual but only partially determines interindividual differences. In other words, your genome makes you a human rather than a round worm, but what kind of a person you will be is only partially determined by your genes.

The second form of genetic determinism is the idea that if a trait has a genetic etiology, environmental intervention will not change it. This view also has no follower in contemporary debates. But a revised version of this view seems to be defensible. In the revised version, environmental intervention is possible if and only if the intervention targets gene activity. The activity of the gene can be targeted or

[134] Sesardic (2005) uses this point to defend the thesis that heritability constrains the modifiability of a trait. I use this with a different aim, as the following sentences show.

the structure of the gene can be changed by the methods of gene editing.[135]This kind of intervention causes no problem for the subtle form of genetic determinism that will be offered below.

The third form of genetic determinism is a subtle one. According to Kaplan, this form of genetic determinism consists of two related theses. The first is the methodological thesis that the level of genes is the best level in the explanation, prediction and control of traits with a partial genetic etiology. Partial genetic etiology means that gene variants are causally involved in the production of the trait, but those variants are not the only cause of the trait. This claim needs further clarification. It can mean two things: 1) The occurrence of the trait requires certain gene variants and certain environmental conditions at the same time, such that if one is absent, the trait is absent. 2) In some individuals, the trait is fully genetic - genes provide a complete explanation. In other individuals, the trait is fully environmental - it is a phenocopy of the genetic trait.

If "partial genetic etiology" denotes the second situation, there is no need for even discussing the issue of genetic determinism because in one part of the population, the trait has a complete genetic etiology and in the other part, it has a complete environmental etiology. Kaplan must be referring to the first kind of situation.

There is also a further, stronger statement underlying the third form of genetic determinism: A trait with a partial genetic etiology should be considered as "primarily genetic" and the method of intervention substantially depends on knowledge of how the respective genes act. To clarify the last point, we might say that, such traits can be modified only by *directly* intervening on gene action.[136] For instance, the

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[135] Gene editing does not furnish a counter argument against genetic determinism, on the contrary, it is what genetic determinism would propose. So, intervention that acts on the activity - not structure - of genes is more relevant to the debate.

[136] Here, the word "directly" is emphasized because a gross environmental intervention with no direct connection to the genes can still be effective at the individual level, by influencing the working of genes. For instance, suppose that poverty causes stress and stress causes abnormal - too low or too high - expression of some genes, which further causes coronary heart disease. Then, the

intervention might consist of inhibiting a transcription factor, which will result in a change in the expression of a certain gene. Intervention is most efficient if it is directed at a level as close as possible to genes.

The third form of genetic determinism, as described by Kaplan, fits well with the revised versions of the first and the second forms. If we combine these three descriptions we arrive at a description of subtle genetic determinism such that:

1) Genome of an organism specifies the species-typical properties fully and interindividual differences partially. This means that species-typical properties have a complete genetic etiology whereas traits that show interindividual variation have a partial genetic etiology.
2) Methodologically, the genetic variants influencing traits with partial genetic etiologies, and the mechanism of gene action at the molecular level, are the best points of departure in the explanation, prediction and control of those traits.
3) Environmental intervention is not useless but the success of intervention substantially depends on the knowledge of the genes involved in the etiology of a trait. In a sense, intervention must be gene-sensitive. For instance, in the case of major depression, drugs that act on specific genes or receptor proteins will be more successful than environmental interventions such as changing one's stressful work environment, if the trait has a partial genetic etiology.

The first thesis should not be interpreted as if there is a categorical distinction between species-typical traits and traits showing interindividual differences. Interindividual genetic variation refers to any kind of genetic difference that occurs in a certain population of a certain species. Interindividual genetic variation affects species-typical properties and there is no limit to the size of effects. A species typical

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government decides to raise the minimum wage significantly and this reduces poverty. In addition, the government's intervention does not depend on a knowledge of the biology of the disease. The reduction in poverty leads to reduced stress and this in turn restores the level of gene expression to its normal levels in individuals. This kind of scenario is consistent with a totally environmental etiology for the disease, even if the genes are involved.

trait - whether it is morphological or behavioral - is a property that develops in *almost* every member of a species (Haraway and Maple 1998, p. 191). These traits need not be species-specific: They may also be observed in other species. For instance, having compound eyes is a species-typical property of fruit flies and many other species. There are mutations that influence the pigmentation (color) and shape of fly eyes. But there are also mutations that completely prevent the formation of the compound eye. In addition, there are lethal mutations which prevent the development of the fly altogether. These mutations all influence species typical traits and they lead to interindividual differences. The central assumption which justifies using such a concept (i.e. species-typical) in the first place is that species-typical properties are not expected to vary much between the members of a species. Variation should be limited to a narrow range of trait values. Extreme environments, as well as lethal mutations can prevent the development of these traits, but in the *normal* range of environmental variation, almost every member of a species will develop those traits. Thus, the first thesis says that common properties of a species develop regardless of the environment and are completely genetic, given that the environmental variation is in the normal range and the residual variation in these traits is partly genetic and partly environmental.

The second thesis concerns the direction of research. It implies that beginning from the genes would be more efficient than beginning from the environment, or any nongenetic influence. This point can be justified on the grounds that genes are involved in almost any biologically interesting phenomenon, whether it be behavior or common disease. But this doesn't mean that the structure and action of genes would give a complete causal story about how traits develop, or how the organism works. That story could still depend crucially on what kind of an environment the organism lives in - the second thesis does not prohibit such a possibility.

The third thesis has direct implications in medical genetics but not in behavior genetics.[137] In medical genetics, the aim is to use genomic data for predicting disease risk and developing intervention techniques. Given the heterogeneity of the genetic bases of complex diseases, the third thesis can be used to justify personalized medicine. The reasoning that leads to personalized medicine is as follows: The common disease has most probably a genetic basis because its heritability is high. But the genetic architecture does not consist of a few common gene variants with high effect sizes. The genetic architecture consists of many genes with small effects or rare variants with high effect sizes. The set of disease related genes also differs between individuals. The person X can get the disease by having a set of deficient gene versions but the person Y can get the disease because she has a different set of defective genes. Common medication would not work because the genetic etiology of disease differs from one person to another. Thus, knowledge of the genome of an individual patient would lead to an individual-specific medical intervention.[138] This doesn't mean that the intervention would reflect the complexity of genetic architecture. A complex genetic architecture does not mean that the intervention would also be complex. It only means that the decision making process in medication would take into account the combination of multiple specific risk factors - most centrally the genetic makeup of a person.

The second and the third theses taken together constitute a roadmap for research and the invention of medical intervention techniques. In this regard, they are more a

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[137] In fact, the third thesis has indirect implications for human betterment. If an individual's genetic makeup determines how to improve his/her conditions, such as increasing the IQ or modifying temperament so as to fit a social standard, the third thesis can be used to defend a personalized behavioral improvement program. In short, such a program would place individuals in the "best" environments - that is, the environments best suited to their genetically determined needs. However, such a program would be just an intellectual way of self satisfaction, given that there are many common maladies the human kind experiences, which can be remedied or prevented without even a primitive knowledge of genetics.

[138] Personalized medicine does not necessarily imply a completely gene based etiology of disease: The reasoning can be enriched by adding environmental risk factors to this hypothetical narrative. But the logic would be similar.

matter of methodological priorities rather than a strict genetic determinist viewpoint. These methodological priorities, however, can be interpreted as the manifestations of a gene centric vision, which will be the topic of the next chapter.

6.9 Conclusion

Genetic determinism is a vague concept. If it is described as a viewpoint akin to Davenport style eugenics, it becomes a belief with no contemporary adherents. To make it more precise and in line with contemporary genetic research, conceptual tools of modern genetics have been invoked. "Gene for X" locution captures the most typical form of genetic determinism - few gene variants explaining the whole variation in a trait - but it is common knowledge that this form of explanation cannot be extended to complex traits such as human behavior. NORs, if they were available in humans, would provide valuable information on the causes of phenotypic variability, however, they cannot be constructed in humans because experimenting on humans is impossible.

Heritability values provide a crude and population specific measure of genetic influence on human traits. Studies performed at the whole genome level were expected to identify the physical basis of heritabilities. Missing heritability problem shows that the molecular genetic basis of heritable variation cannot be easily captured. The picture emerging from GWA studies is that multiple gene variants with very small effects - Fisher's infinitesimal model - is valid for almost every behavioral trait (Chabris et al. 2015). In addition to polygenic inheritance, another complication comes from the heterogeneity of the genetic bases of these traits. Genetic determinism concept should be replaced by the concept of genetic determination. Because the interesting question is not whether genes have any effect on behavioral phenotypes or whether behavioral phenotypes are fixed by the genes. The interesting question is how genes influence phenotypes, including behavior.

So far, all focus was on the effects of gene variants on the variation of phenotypes - the effects of environment have been neglected. Genetic research depends on

minimizing the effects of environment so as to make genetic effects visible. Methodologically, this might be inevitable for genetic research, but this methodological point is easily transformed into a full blown theory of the primacy of genes. This biased viewpoint, namely the gene centric perspective is the topic of the next chapter. The concept of information will once again occupy the center stage because the concept of information is used to justify the gene centric perspective.

CHAPTER 7

GENE CENTRISM, INFORMATION AND GENE CONCEPTS

7.1 Introduction

The last century has been called "the century of the gene" (Fox-Keller 2002). From the rediscovery of Mendel's laws in 1900 to the beginning of the Human Genome Project in 1990s, every field in biology and even psychology has come into the zone of influence of genetics.

Gene centrism is the viewpoint that genes have a more fundamental role in development compared to nongenetic factors and more generally, it is the view that genetic material is the primary source of order in the biological world. This doesn't mean that genetic material has occult properties. DNA is a physical structure like everything else in an organism and its interactions with other molecules are also ordinary physical reactions. The theoretical justification for the primacy of genes invokes the concept of information because only DNA is said to carry information. The sense in which informational concepts are used in biology is ambiguous. The ultimate function of information metaphors in biology is to make the field look more unified than it really is.

Gene centrism is tightly related to genetic reductionism. In fact, gene centrism can be seen as a natural consequence of genetic reductionism. Genetic reduction is an explanatory strategy which favors genes over other causes of phenotypes. In this strategy, biological traits are seen as ephemeral manifestations of deeper genetic causes. Trait differences can ultimately be traced back to genetic differences. Evolution can be represented at the level of genes and phenotypes are mere byproducts of gene replication. Genes are the simple and invariant causes of phenotypes. Tracking genes is tracking phenotypes. Genetic determinism – the idea

that genes singlehandedly determine the phenotypes of adult organisms – can be seen as an unintended but highly likely consequence of this explanatory strategy. If you can explain and predict phenotypes by means of genotypes alone, it is natural to think that phenotypes are causally determined by genotypes.[139]

Mendel was following this strategy when he traced the invariant mathematical relations between hereditary factors and the distribution of corresponding traits in the offspring. Morgan and his students were employing the same strategy when they identified and mapped these factors onto chromosomes. The single locus biallelic models of early evolutionary genetics were simplifications in the same spirit. Fitness value of each allele was fixed; complex relations between different loci were ignored. Fixed fitness values along with other variables such as population size and allele frequencies were used to explain the dynamic phenomenon of evolution. Ernst Mayr (1959) ridiculed the whole enterprise as "beanbag genetics".

Meanwhile, the strategy was at work in its whole glory in molecular biology. DNA was identified as the bearer of genetic information; its function was to act as a template in protein synthesis. Proteins were the ultimate bearers of biological function. Their primary structure (amino acid sequence) determined their 3D structure which determined their function. The mechanism of protein synthesis was the causal bridge between genetic information and biological function. The machinery was universal, thus, biology gained the status of exact sciences such as physics and chemistry.

In the 1960s Jacob and Monod discovered that the capacity of organisms to adaptively respond to changing environmental conditions also lied in the genetic material: protein synthesis was regulated by switching genes on and off and the switches

[139]The chain of reasoning is as follows: Genetic reduction is a kind of causal explanation. Gene variants are not mere predictor variables that covary with the phenotype of interest. They are causes of phenotypic variation. Thus, if a phenotype is reduced to the presence of a certain variant, it is causally explained by the presence of that variant. The relation is deterministic on the assumption that all other causally relevant variables are fixed.

(operator regions) were on the DNA. Thus, the backbone of the molecular explanation of life was in place: DNA sequence determines protein sequence; protein synthesis is regulated by environmental triggers that activate or inhibit certain switch mechanisms that reside on the DNA.[140] Environment acts locally: environmental factors should translate into intracellular molecular changes in order to act on those switches. The effect of the environment has been reduced to pressing this or that trigger. Triggers were in the genes, specific response mechanisms were in the genes. Genes were at the center stage in every biological process.

The opposite of this thesis is that genetic and nongenetic causes of biological processes are on a par. The so called parity thesis – or "the causal democracy thesis" – is the statement that there is no fundamental distinction between different causes of development. Proponents of the parity thesis brought every argument in favor of the primacy of genes under critical scrutiny.

The Human Genome Project and the debates revolving around it is a good starting point to see gene centrism in practice. In the theoretical side, information concepts, the parity thesis and new gene concepts will be our focus. Lastly, we will deal with the question of why DNA still has a special role in some explanatory contexts.

7.2 Human Genome Project and the Primacy of DNA

In 1990s, when the Human Genome Project was underway, the hopes were high. Popular science books were full of exaggerated claims such that the knowledge of the genome would teach us the essence of being human, why we get ill, why individuals are different, how diseases can be cured, etc. I won't list every such statement, because they are already documented in Richard Lewontin's "The Dream of the Human Genome" (2001). One point was essential to all of those hopeful comments: DNA is so special in biological processes that knowing its structure will provide the

[140]Here, environment is considered to include all nongenetic variables such as the metabolites in a cell and external influences.

most valuable information in understanding life. James Watson, the codiscoverer of the double helical structure of DNA with Francis Crick, was one of the most ardent defenders of the gene centric perspective. In his defense of the Human Genome Project, he stated that best strategy in medicine and psychiatry is to identify the genes that cause disease (Watson 1992a). His focus on genes excluded other types of research.

> If you can study life from the level of DNA, you have a *real* [emphasis added] explanation for its processes (p. 164)…
>
> The fact is that understanding how DNA operates provides an enormous advantage over working only with proteins or fats or carbohydrates (p. 166)…
>
> It is pretty clear that manic depression has a genetic cause. Several scientists thought they have located the gene on a chromosome. But then it got lost, and *so long as it is lost, we are lost* [emphasis added] (p. 167)…
>
> I believe in neurobiology and have tried to help raise money to support the field. But I do not believe that its current approaches will necessarily lead to the *real, deep* [emphasis added] cause of manic depressive disorder (p. 167).

James Watson was the first director (1991-1992) of the National Center for Human Genome Research and he was well known for his straightforward (sometimes annoyingly arrogant) style of expression (Judson 1979, Crick 1988). However, "getting the genes" was a common stance of the defenders of the project. Walter Gilbert (1992) defined the project as a search for the holy grail of biology. Gilbert (Ibid) had assumed that once the sequence was at hand, the information residing in the DNA would allow the computation of the embryo. Computing the embryo is equivalent to understanding the essential biochemical processes guiding development. Gilbert proposed that if computational methods to read DNA data can be created, biology will become an exact science like physics. Sequence data will give the essence of a species. From this invariant – or averaged – essence, anatomy, physiology and behavior of a "normal", "prototypical" member of the species will be computed by means of the computational methods plus the laws of physics and chemistry.

These ambitious claims created a heated discussion about the prospects of the project. The critics of the project shared one idea: DNA sequence data alone won't give us the answers about disease, behavior, etc. and the unwarranted belief in the opposite was more a matter of ideology than science (Lewontin 2001, Tauber and Sarkar 1993). Before the beginning of HGP, molecular biologists and geneticists had already learned that the "few (genes) to few (phenotypes)" perspective of Mendelian genetics was unsuitable for almost any kind of biological trait such as a medical condition like cardiovascular disease or major depression. But DNA sequence was advertised as more fundamental, deeper and "the" real cause of complex phenotypes. The complex relations between genes and environment were omitted. Epigenetic mechanisms of gene regulation were ignored. RNA splicing and posttranscriptional modification, tissue specific protein synthesis and all other confounding factors were ignored. The focus was solely on sequence and the promises were too great to be satisfied by sequence alone. Although such confounding factors were already known by scientists such as the most straightforwardly reductionist proponent of the project, James Watson (1992 b), their importance was almost always papered over the cracks.

The results of the Human Genome Project refuted these exaggerated claims. The draft sequence of the project was published in 2001 and the project was finished in 2003. The number of genes in human genome was estimated to be approximately 30000 in 2001 (Venter et al). The following big project, ENCODE, was aimed at taking a deeper look at the protein coding 1% of the genome. Up till now, from such genome wide studies and more specialized ones, a picture such as this has emerged (The ENCODE Project Consortium 2007, Pearson 2006):

1. There is ubiquitous RNA production in both coding and noncoding portions of the DNA. Some of these RNAs (e.g. small interfering RNAs) have known functions in the regulation of protein synthesis but most has no known function.
2. There are many levels at which genes influence the production of specific phenotypes. Protein structure is just one of them. The timing and amount of

protein and RNA production in specific tissues are among the most important determinants of phenotypes.

3. The same gene product can have many different functions in different biological contexts.

Given these points, it is safe to conclude that the results of HGP and following projects did not support a simple form of genetic explanation. The "few to few" connections expected to be found between gene variants and phenotypic variation were not found. Sequencing the genome was far easier than reading its meaning (i.e. understanding its function).[141] But the importance of genes was not diminished by these results. Gene centrism survives. Thus, it is compulsory for us to understand why genes have gained a privileged role in biology.

The results of HGP and related projects clearly showed that the relation between DNA sequence and organismic function is not straightforward. But as the history of genetics shows, it was the capacity of the genetic material to help in building a functioning organism that could justify the primacy of it. Schrödinger (1951) speculated about the aperiodic crystal not because of its physical structure but because of its explanatory role. The aperiodic crystal was hypothesized because it would carry the heritable information that specifies the adult organism. The double helical model of DNA was not important for its sugar backbone or the possible heterogeneity of its inner nucleotide sequence. The sequence was only important because it could determine the inner workings of the organism. But the specific ways in which genetic material determines phenotypes were not specified, except at the level of protein synthesis. Information talk, and especially the idea of a genetic program, is a shorthand for saying that genes specifically determine the phenotype of an organism. Determination by a program is an abstract concept of causation. It is abstract in the sense that the structure of the material realizers of the program's

[141] Understanding function requires a three-step process: identifying phenotype (e.g. disease) genotype associations (i.e. the top-down approach), identifying the molecular pathways in which a certain gene product is involved (i.e. the bottom up approach), and integrating this knowledge into a framework of development.

instructions is important only to the degree that they play this informational role. This abstractness gives the informational framework the power to act as a unifying theory of biology. Whenever a new mechanism is discovered, it can be integrated into the program. Every detail about the actual mechanisms connecting genes to phenotypes can change but the information idea remains.

7.3 Information in Biology

In the second chapter, the origins of information concepts in biology were mentioned. It was said that there were two types of information concepts in biology: information as sequence and information as regulation. The sequence concept of information was first formulated by Francis Crick in the Central Dogma of Molecular Biology. According to the dogma, information is the precise determination of amino acid sequence in a protein by means of the nucleotide sequence of DNA. The cybernetic concept was developed by Jacob and Monod in early 1960s. In this concept, information is defined as regulation by means of a signal. The signal enters into positive or negative feedback loops where it acts as an activator or inhibitor. One important concept Monod (1972) used was gratuity. Gratuity means that the biological function of the signal is partly independent of its physical structure. Gratuity follows from allosteric structure of regulatory proteins.

Sarkar (1996) claims that information concept had a heuristic role in a limited period. No formal theory of information played a positive role in the progress of molecular biology or genetics. If this is the case, it becomes more urgent to explain why information talk in biology still persists and why biologists act as if the information concepts are essential to theorizing about living things.

Many biologists with an eye on theory have defended the use of informational concepts in biology. Ernst Mayr has defended the uniqueness of living things on the grounds that organisms develop according to a genetic program (Mayr 1961, 1982, Mayr 2004). John Maynard-Smith (2000) claimed that DNA carries symbolic information. Biochemist Daniel E. Koshland (2002) cited "program" as one of the

definitive features of life. George C. Williams claimed that there is a codical domain in addition to the material domain and codical domain is defined by informational terms such as "bits, redundancy, fidelity and meaning".(1992, p. 10)

An exhaustive list of authors and an analysis of their diverse ideas on the concept of information is not intended here. This short list shows that when biologists theorize, they frequently use informational ideas. Information concepts in biological theorizing function as tools for demarcating organisms from inorganic nature and genetic causes from the rest of the developmental factors.

We can categorize the usage of information and related concepts in biology as such:

1) Information as data.

This is what bioinformaticians mean when DNA sequence is said to carry information. "Information as data" is a theory free description. It doesn't imply any causal structure or any privileged role for one kind of source in some causal explanation. Any data set such as DNA sequence, set of RNAs, proteins or metabolites in a tissue, medical history, etc. carry information in this unproblematic sense of the term. This usage fits well with Shannon and Weaver's mathematical theory of communication. In this theory, information is defined by systematic covariance between a source and a message. For example, a thermometer reading (message) carries information about local temperature (source) because it covaries with it. The message can be used to predict the state of the source, but the message doesn't have to give a causal explanation about why the source is in that state. For instance, having a certain allele (message) can be correlated with having a disease (source). Knowing that an individual has the allele increases the accuracy of prediction. But the allele might have no direct causal connection to the disease. So, "information as data" can also be called "information as covariation" or "information as predictor".

2) Information as coding.

This usage is more specific than the first one. It concerns the relation between DNA sequence, RNA sequence and protein sequence. In this concept, there is explicit causal structure. Information is precise sequence and it follows from DNA to RNA and to protein. It is called coding because there is a set of physically arbitrary rules of translation (i.e. genetic code). This sense of information is also unproblematic, at least in prokaryotes.

3) Information as regulation.

Organisms adapt to their environments by responding to certain environmental variables. These responses, if they will be stable, always involve a change in the synthesis of proteins. For instance, in long term potentiation of neural cells, structural changes in the cells occur via changes in protein synthesis (Kandel 2001a). Here, the genome acts as a static resource whose information content is dynamically interpreted by the cell. Environmental variables act as information sources as well. In this sense of the term, the focus is on the information processing capacities of the whole cell (or organism) rather than the static structure of the message. Information processing amounts to adaptively responding to the message. The problem with this "organism as information processor" metaphor is that it adds nothing to our understanding of causal mechanisms that bring about those adaptive responses. It is just a redescription of them.

4) Information as genetic program.

This is the strongest and most problematic usage of information concepts in biology. It is a combination of the second and third concepts. In contrast to the second definition, genetic program is not limited to the sequence determination of proteins. Its zone of applicability can reach any biological trait one can think of. But prototypically, the program idea is about the "essence" of a species. Essence here means what is common to most members of a species.

Program metaphor is invoked to explain the regularities in the outcomes of the developmental process. A chimpanzee begets a chimpanzee whatever diet it is exposed to. Unless development is drastically perturbed, e.g. by a mutation or abnormal environment, species-typical morphology, physiology and behavioral traits develop reliably.

This information concept is the strongest because it implies – or it seems to imply – a deterministic and reductionistic vision of development. The connotations of programming – albeit falsely – include inflexibility in performance (Dawkins 1982). A program may be open ended – its instructions may not lie solely in the genome and new instructions may be incorporated by learning – as Mayr (2004) suggests. But the genetic program can't be an open program because of the noninheritance of acquired characters – no new instructions can be incorporated into the genome, except by means of mutations. That is why some thinkers prefer the term "developmental program" rather than genetic program.

One problem with the program metaphor is that every physical event can be said to be the execution of a program. Think of a rolling stone. Its movements can be simulated by means of a program but does this mean that rolling is the execution of a program, in any interesting sense of the term? I don't think so. The fact that some process can be modeled as the implementation of a program does not imply the process itself is implementing a program. There is no metaphysical distinction between "genuine algorithmicity" and "pseudo algorithmicity" but it is still useful to keep in mind that the prototypical properties of a computer program are not realized in living systems, except perhaps in the central nervous system.[142]

A definitive feature of a program is that it can be described as a set of explicit and specific instructions – i.e. by an algorithm. Instructions are usually conditional statements such as "do such and such operations on variable Y if the variable X takes

[142] For a discussion about "genuine algorithmicity", see Bolender 1998.

such and such values, otherwise...” The independent variable (input), the dependent variable (output) and the operations to be performed are explicitly described. But in development as well as cellular metabolism, there is no such clear-cut distinction.

The defenders of the information metaphor such as John Maynard-Smith (2000) are well aware that there is no strict isomorphism between genetic material and a computer program. According to Maynard-Smith, the metaphor is used to capture a "qualitative similarity" between two fields. But qualitative similarity allows one to compare almost any kind of regular causal structure to a program, as the "rolling stone" example is intended to show. If a concept is applicable to almost anything, the concept loses its significance. But when the genetic program is specified such that its proper inputs and rules of computation are made explicit, the metaphor is turned into a concrete model. Then, biology would be a science about finding the rules and proper inputs of this program because this program, or programs in different species, would be the concise description of an organism. Since it resides in a localized molecule that can be studied in isolation, this would give a great boost to our understanding of organisms. The parity thesis proposed by Developmental Systems theorists is a reply to this closed, self-sufficient, gene centric system of explanation.

7.4 Causal Parity Thesis

Developmental Systems Theory (DST) proponents reject the whole conceptual structure of gene centrism. DST is not a unified theory, contrary to what the name suggests. Rather, it is a connected bundle of theoretical and research approaches towards developmental and evolutionary phenomena. In contrast to the gene centric perspective, DST proponents don't locate the source of biological order and variation solely in the genetic material.

Some DST theorists such as Oyama (2000), Griffiths and Gray (1994) and Richard Lewontin (2000, 2001) have defended the parity thesis, by means of interrelated arguments.

In the fundamental text of the field, Susan Oyama (2000) offers a conceptual restructuring of the whole field. According to Oyama, gene centric biology considered DNA as a control center in development. Genetic material is the ultimate source of organismic form whereas other factors are seen as mere building blocks, which are organized by the information carried in the genetic material. According to Oyama, genetic material by itself can't explain the origin, maintenance and differentiation of organismic form. Genetic material is part of an interactive system which maintains and reproduces itself by using genes and nongenetic resources. Thus, according to Oyama, it is not the case that genes are unimportant. They are important only to the degree that they play their role in this system of interactions. One important property of developmental systems is that there is no homunculus in the organism that acts as a control center in development.

Here, parity means that genes and nongenetic factors are coupled in development to such a degree that attributing them context-independent, intrinsic functions – e.g. an informational role – is misleading. For Oyama (2000), it is valid to say that genetic variation is the source of phenotypic variation in some contexts. But it is misleading to defend general statements such as "genetic material is the source order in the world", "gene is the only unit of selection" or "genes carry information whereas other factors are mere building blocks".

Information concept carries an essential role in the gene centric framework. According to Oyama, gene centric vision treats biological information as something which can exist independent of the material bearers of it. It requires material bearers to become an efficient cause but it still has "a kind of atomistic autonomy as it moves from place to place, is gathered, stored, imprinted, and translated." (2000, p. 1).

Oyama claims that information is something generated on the go, not something that resides in the genes and actualized when interpreted. In contrast, information is built in the process of development by means of interlocked contingencies. Every step in the developmental process is conditioned by the prior steps.

In DST, DNA doesn't carry information about the adult organism in the sense that a blueprint carries information about the finished building. Rather, it is a *resource* whose functional elements (e.g. exons, regulatory regions) play their roles only in response to some specific aspect of environmental input. Conceptualizing DNA as a resource of information rather than a center of control or a set of developmental instructions is a big step in the history of the concept of genetic causation. The gene centric vision had treated development as a black box, both in classical genetics and evolutionary genetics. DST vision opens this black box and arrives at the conclusion that control is distributed across interactants and reliability of developmental outcomes don't depend on a molecular homunculus.[143]

In Oyama's vision, parity thesis has a heuristic role.[144]It has a heuristic role when it helps in seeing what was invisible in the gene centric framework. While discussing a debate between DST theorists and more traditional "interactivists" (Sterelny, Smith and Dickison 1996), she makes the following remarks[145]:

> Notice that it is the parity move that invites these conjectures by making it thinkable that a burrow could be an evolutionary 'replicator' (roughly, a self-reproducer, though Sterelny et al. revise this; the model is the selfish gene). One takes the reasoning being used for some kind of developmental resource,

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[143] Here, homunculus refers to a center that directs development: the DNA. In the history of biology, homunculus first appeared as a miniaturized human being contained in a sperm cell and which develops into an adult human, in prthe mteaphor was used to describe early preformationist theories of development.

[144] The substantive and heuristic uses of a concept are distinguished by Sahotra Sarkar (2000) as such: If the concept plays a role in the construction of a theory or a model, etc. but it doesn't occur in the constructed entities explicitly, that concept has a heuristic role. If is occurs in the theory or model (or law, etc.), it has a substantive role. As an example, consider the case of James C. Maxwell's electromagnetic equations. At some point in the ontogeny of these equations, Maxwell had used vortexes and idle wheels in order to represent the electromagnetic field (Nersessian 2008). But these don't appear in the formal theory. They have a heuristic role but not a substantive role. The mathematical tools developed to model vortexes have both of these roles.

[145] Traditional interactionism is the view that genetic and nongenetic factors interact in development but there still is a fundamental, context-insensitive way to delineate their functions. It is the spirit of our age, concerning genetic causation.

> in this case genes, and asks whether it can be used for others as well (Oyama 2000, p. 240).

In the gene centric perspective, only genes are seen as replicators whereas organisms and their products (e.g. nests) are seen as interactors. But if the parity thesis is taken seriously, one can see that a function that was exclusively attributed to the genes (i.e. replication) can also be realized by a more inclusive set of factors.

This set includes cellular epigenetic inheritance system (chromatin marking), endosymbionts, structural inheritance (e.g. the 3D structure of ciliary rows, membranes acting as “templates" in membrane production) as well as cytoplasmic gradients (Jablonka 2001; Oyama, Griffiths and Gray 2001). These systems of inheritance are not similar to the genetic inheritance system in many respects. The essential difference is that there is no dedicated replication machinery in these systems, but this is not a problem for the DST approach. Exact replication of digital information (i.e. copying) – as in the DNA sequence replication – doesn't occupy a central theoretical role in DST.

DST theorists call this revised and inclusive view of heredity as "extended inheritance" (Ibid. p.3). Extended inheritance refers to the revisionary views that:

1) There are inheritance systems apart from the genetic inheritance system, as exemplified above.

2) More importantly, inheritance extends beyond the individual organisms. Even an external resource can be considered as part of an inheritance system, if it is transmitted across generations.

According to DST, inheritance should be relativized to the developmental system. Inheritance explains the similarities between parents and offspring. Inheritance is not making copies of oneself. The transgenerational stability of phenotypes (e.g. species-typical morphology) has traditionally been explained only by the similarity of the

genetic material. According to DST, any factor that contributes to this stability and is replicated in this process is part of the inheritance system.

Given these points above, it might be thought that the parity thesis rejects any distinction between the specific mechanisms, reliability levels (i.e. exact copying vs. mere similarity), time-frames (i.e. the number of generations a property is transmitted) and developmental effects of different inheritance systems. This is not the case.

Causal parity in DST "does not imply that there is no difference between the *particulars* of the causal roles of genes and factors such as endosymbionts or imprinting events. It does assert that such differences do not justify building theories of development and evolution around a distinction between what genes do and what every other causal factor does." (Oyama, Griffiths and Gray 2001, p. 1).

Informational concepts were invoked to defend the asymmetrical relation between genes and nongenetic developmental factors. According to Griffiths and Gray (1994), there is a symmetrical relation between genes and nongenetic factors if information is what the mathematical theory of communication meant it to be. Genes, in this perspective, are just one source of heritable information. The opposing view is that only the genome can transmit such information, even if all other developmental resources are as necessary for normal development:

> "No biologist in his right senses will forget that the blueprint contained in the genome requires innumerable environmental factors in order to be realised. . . . During his individual growth the male stickleback may need water of sufficient oxygen content, copepods for food, light, detailed pictures on his retina, and millions of other conditions in order to enable him, as an adult, to respond selectively to the red belly of a rival. Whatever wonders phenogeny (sic) can perform, however, it cannot extract from these factors information that simply is not contained in them, namely the information that a rival is red underneath." (Lorenz 1965, quoted in Griffiths and Gray 1994, p. 281**).**

In this passage, Lorenz makes a fundamental distinction between genetic and environmental inputs to the developmental process. Environmental factors are presented as unspecific background conditions for normal development to occur. But the species-typical properties of organisms, including innate behavioral responses, are in the genes. One can compare this to the development of language faculty in humans. Gene centric perspective accepts that environmental input – whether it is linguistic input that shapes one's ultimate competence in his/her native language or less specific factors such as food – is a necessary part of the development of the language faculty, but the ability to learn language is in the genes. It can't be acquired from the environment.

Griffiths and Gray believe that there is no dichotomy between genetic and nongenetic information. Their point depends on the meaning of information in the mathematical theory of communication. As told before, information in this theory required correlation between the states of two things (i.e. source/sender and the receiver) and channel conditions. We can reformulate the primacy of genes by considering genetic material as the message, all nongenetic factors as channel conditions and the adult organism as the receiver. In this sense, DNA carries information about the adult organism (the developmental outcome), all other factors involved in development function as channel conditions.

Alternatively, genetic material can be presented as providing the channel conditions and environment be taken as the message. This is why the DST perspective offers symmetry. Message and channel conditions can be replaced with suitable adjustments.

Lorenz and most gene centric thinkers couldn't accept this symmetry because their concept of information did not imply mere correlation (Ibid. p. 282). Their information concept was semantic, as exemplified by the word "blueprint". A blueprint is not only correlated with the finished building. It carries unambiguous

instructions and it has a *normative* relation with the finished building. If the finished building is not like what is expected, the error is attributed to factors other than the blueprint itself. The house can be said to misrepresent the blueprint. The message has an intrinsic meaning, independent of how it is interpreted. But the channel conditions – the building blocks, methods of building, workers – have no such relation to the finished product. In the case of development, the relation between the genetic information is this kind of semantic relation. If the environment is altered so as to inhibit normal development, the message contained in the genome is still there but it was just misinterpreted due to abnormal channel conditions.

Semanticity of genetic information is tied to natural selection. The male stickleback's response to the red belly of a conspecific is an adaptation in the phylogenetic sense: It is the product of a long selective process in which the ancestors of modern sticklebacks *genetically* varied with respect to their responses and individuals that had the suitable genetic propensity to respond outreproduced others. This gradual selective process is commonly compared to programming by Neo-Darwinians such as Dawkins (1976), John Maynard-Smith (2000). Natural selection gradually changes the information content of the genome and produces genetically encoded, adaptive behavioral patterns.

According to Griffiths and Gray (Ibid.), information, in the sense of systematic dependence is a symmetrical relation but there still is a practical way to say only one type of resource carries information: holding the state of the other sources constant. For instance, it may be correct to say that an allele carries information about a trait if developmental conditions and the genetic background are held constant. But one can hold the allele constant and vary other sources as well. Thus, there is no fundamental asymmetry here, only a change in perspectives.

Lewontin, in his foreword to Oyama's (2000) book, criticizes the gene centric perspective by three interrelated lines of argument. I call these three arguments as the argument from experimental bias, argument from the insufficiency of DNA and the argument from the stochasticity/complexity of development. These arguments are not

defenses of a form of parity thesis per se. They are aimed at showing the weakness of certain aspects of the gene centric perspective.

The first argument can be summarized like this: Genetic research into the functional effects of genes depends on gene alterations of major effects in controlled environments. Knowledge gained from this type of research can't be extrapolated to the study of natural variation.

According to Lewontin, dominance of gene centrism can be partially explained by the biases created in the practice of genetics. He claims that Mendel's original aim was to analyze inherited *differences* by statistical methods. Mendel found that the populations could be dissolved into different types whose transmission patterns could be analyzed in hybridization experiments. But, when he explained the *types* by means of *factors,* he introduced a kind of preformationism into genetics: factor differences corresponded to trait differences and *factors became causes of the traits*. In this way, genes (factors) became ultimate determiners of phenotypes.

According to Lewontin, the explanation of a difference may say nothing about the ontogeny of the trait. In classical genetics, only differences matter. Genes are represented according to the phenotypic differences they are coupled with. For instance, the gene for purple eyes in *Drosophila* is not the sole factor responsible for the development of purple eyes but it explains the presence of purple eyes in some flies in contrast to, say, red eyes. According to Lewontin, the experimental techniques of Mendelian genetics produced theoretical biases which show up as exaggerated claims about the causal efficacy of genes.

The strong and unambiguous effects of allele substitutions in Mendelian experiments can't be extrapolated into natural variation in complex non-Mendelizing traits. Experimental genetics requires that the experimenter holds as many variables constant as possible, in order to make the effect of the gene substitution as visible as possible. For instance, in knockout experiments – those in which a gene is completely silenced – a drastic change in one locus is created and the resultant phenotype is

examined at many phenotypic levels (e.g. mRNA synthesis from other loci, gross anatomy, etc.). Remaining loci and environmental variables are held constant by using inbred lines and controlled environments. For Lewontin, this creates a bias as such:

> The actual path taken by the geneticist is precisely to study only those gene alterations that have major effects on the development of their test organisms while growing those organisms in controlled environments that *maximize the developmental effect* [Emphasis added] of the gene alterations. So, only a small proportion of all single gene mutations known by Drosophila geneticists are so-called Rank I mutants, that is, mutants in which every individual carrying the genotype is unambiguously different from the nonmutants. And even these mutations are often unambiguous in their effect only at a particular temperature or humidity and only if the background genotype is selected to maximize the mutational effect. Yet these extraordinary situations are the only tools available to the developmental geneticist who is supposed to be interested in the production of form and function. (Lewontin 2000, p. xiii).

According to Lewontin, the size and unambiguity of the effect is not an intrinsic property of the gene alteration but it is the response of the whole developmental system to that alteration. Effect size depends on the genetic background and the environment. In natural populations, it is impossible to homogenize or randomize environment and genetic background. If the effects of genes are contingent upon the environment and the genetic background, then it can be said that genes and nongenetic factors are on a par in development.

The insufficiency of DNA argument is a critique of the idea that DNA is a self-replicating and self-active molecule. Self-replication is the ability to make copies of oneself and self-action is to create an organism by oneself. However, DNA could not replicate itself in the absence of DNA replication mechanism composed of proteins and DNA could not produce the entire organism by itself (Lewontin 2001 p. 141). For Lewontin (2000), DNA is the most inert molecule in the cell. DNA is a passive information source which gains functionality only when it is "read" by the transcription machinery: "So DNA becomes 'information' about the organism only in the actual process of cell function." (Ibid. p. xiii).

The third line of argument Lewontin offers depends on the complexity and stochasticity of development. Organism is a middle sized object which is influenced by many weak forces, both from within and without. Developmental process is sensitive to initial conditions such as the absolute number and distribution of key developmental proteins in the egg cell. Given this complexity and stochasticity, even a complete knowledge of the genome and the environment doesn't make it possible to predict the phenotype of the adult organism. Sydney Brenner - in 1982 - and Walter Gilbert (1992) had claimed that with a complete knowledge of one's DNA sequence and with the relevant computational tools, one could compute the embryo from this information alone (Lewontin 2000, p. vii). But if development is a stochastic process, this becomes impossible. And if biological specificity is not in the genes – or the environment – and it is partially a matter of chance fluctuations, DNA is on a par with nongenetic factors including chance events in the determination of the ultimate developmental outcome.

Whatever specific arguments were used in favor of parity, the primary aim was to oppose the closed, gene based explanatory trend in biology. But the privileged role of DNA can still be defended with respect to a particular process, namely, protein synthesis. Kenneth Waters' (2007) actual difference making concept is aimed at justifying this role.

7.5 Actual Difference Makers and the Parity Thesis

Kenneth Waters (2007) proposed a special concept to refute the parity thesis with respect to protein synthesis (i.e. "the insufficiency of DNA argument"). According to one version of the parity thesis, genes play their role in development in conjunction with nongenetic factors. Since development can't occur without one of these kinds of factors, there is no need to attribute a privileged role to genes. A sexually reproducing organism doesn't inherit only the chromosomal DNA from its parents. The egg cell contains many proteins without which gene expression and protein synthesis are impossible. So, the protein synthesis machinery is as essential as the DNA itself in development. For the developing organism, not only DNA or the proteins from the

egg cell are enough. Development needs external resources such as nutrients, a certain range of temperature, oxygen, etc., which should be provided from the environment. The proper functioning of genes depend on these factors. Gene expression is sensitive to environmental variables. Genes and environment interact at every level of development. For these reasons, there is no fundamental difference between genetic causes and nongenetic causes. Genetic causation is not a special type of causation, the resultant organism is a consequence of the complex interaction between many factors.[146]When many causes interact to produce the outcome, are we ever justified in picking some and saying that it is the cause?

In fact, specifying individual causes of events is one of the recalcitrant problems of philosophy since J. S. Mill. In the real world, as opposed to simplified models of it, events are usually complex. Real world events happen, as J. S. Mill suggested, by the conjunction of many negative and positive conditions.[147] A factory fire is such a complex event but when such an event occurs we still ask the question "what is the cause of the fire?" To say that "the fuse box explosion is the cause of the fire" is a satisfactory explanation in many cases. But for a broken fuse box to be the cause of a fire, many other conditions, some negative and some positive, should be present: Fire extinguisher *doesn't* work, there are flammable materials and oxygen in the surrounding, the warden falls asleep, etc.

According to Mill and many philosophers of science, it is only pragmatically reasonable to distinguish one factor among this interactive jungle and call it "the

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[146] Defenders of the parity thesis differ on their views on what interaction amounts to. In Susan Oyama's "constructive interactionism", interaction is not a relation between independent factors. Factor theories of causation depend on the idea that factors can be defined independent of the contexts/interactions they occur in. Oyama's version of parity thesis rejects this. Lewontin's "dialectical biology" also rejects factor theories. But Kim Sterelny, Peter Godfrey-Smith and Philip Kitcher interpret interaction as a relation between independently identifiable factors.

[147] According to Mill, the crowning one of the many conditions as the cause of an event is philosophically unjustified: “The real Cause, is the whole of these antecedents; and we have, philosophically speaking, no right to give the name of cause to one of them, exclusively of the others.” (Mill 1981, p. 328).

cause of the event". Here, pragmatic means that the question and answer depends on the context and the problem that is intended to be solved. For instance, in a factory fire, distinguishing the cause is also finding out where to intervene or whom to blame. One can't blame oxygen and it is more costly to prevent fires by making the factory oxygen free than simply changing the fuse box or firing the warden. In addition, the factory had worked like clockwork for years and some *change in conditions* must be responsible for the *unusual event*. Searching for the cause of an unexpected event is searching for the *specific difference* between the states of the factory in which fire didn't happen and those in which it did. For Waters, to ask for the cause in such situations is to ask for the actual and specific difference that made the difference between these states. If we return to our factory example, oxygen and flammables were already present in the days before; the warden had fallen asleep many times before the event. The only specific difference between the states without fire and those with fire is the explosion of the fuse box.

Waters calls this concept of cause *actual difference maker* (ADM). ADM comes in two kinds: "the ADM" and "an ADM". Waters defines "the ADM" as follows.

"X is the actual difference maker with respect to Y in population p if and only if:

(i) X causes Y (in the sense Woodward's manipulability theory).

(ii) The value of Y actually varies among individuals in p.

(iii) The relationship expressed by 'X causes Y' is invariant with respect to the variables that actually vary in p (over the spaces of values those variables actually take in p).

(iv) Actual variation in the value of X fully accounts for the actual variation of Y values in population p (via the relationship X causes Y)." (Waters 2007, p. 567).

Waters' ADM concept is defined in relation to a population. It is not about single events or individuals. There should be a set of comparable things (i.e. events, individuals, states, etc.) in order for a difference to be specified. Thus, it is not aimed

at explaining the ontogeny of some individual object or an event. "p" is the population of comparison in which differences can be singled out. Now, we can continue with explicating the four conditions of being the actual difference maker.

(i) presupposes Woodward's manipulability theory of causation. According to that theory, when we say that X causes Y, we say that an actual or possible *intervention* on the value of X will systematically change the value of Y under some conditions. The theory has been developed specifically for capturing the use of causal concepts in special sciences (i.e. sciences other than physics and chemistry). Causation means neither necessity nor sufficiency in this theory. The phrase "under some conditions" is meant to capture the fact that causal generalities can break down out of those conditions.

(ii) means that if there is no actual variation in the effect variable, one can't pick out an actual difference maker. Thus, if a population is made of individuals identical with respect to the effect variable, there is no ADM in there. It is fairly clear that two factories with no fires would not be the best comparison population for picking out some cause of factory fires.

(iii) states that variables that actually vary in the specified population don't change the invariant causal relation between X and Y. Suppose that X takes values x1, x2, ... and Y takes values y1, y2... The invariant relation can be expressed by the one-to-one function {<x1, y1>; <x2, y2> ;...}. Further suppose that there is a variable Z which takes the values z1, z2 ... If variable Z interacts with X or Y in such a manner that its actual variation in p breaks the invariant causal relation between X and Y, then X is not the actual difference maker in this population. In the factory example, it might be supposed that the presence and absence of flammable substances in the vicinity of the fuse box is actually varying in the population of comparison and this interferes with the causal relation between fuse box explosion and fire. If this is the case, fuse box explosion is not the actual difference maker concerning the presence or absence of fire in the comparison population.

(iv) means that the only causal factor that explains the variation in Y is X. This criterion is one of the two differences between "the ADM" and "an ADM" concepts. An ADM explains only some part of the variation in the effect variable. For instance, think of a population of flies in which some flies have white eyes due to a recessive mutation, some have white eyes due to their diet (i.e. phenocopies) and the remaining flies have red eyes. In this population, variation in eye color is due to two sources: the mutant allele and diet. Both are actual difference makers. If the white eye phenotype had been solely due to the mutation, the mutation would be the actual difference maker. In a sense, "an actual difference maker" is "the actual difference maker" in some proper subset of the population. If we exclude whites due to diet, white eye mutation would be the actual difference maker in the remaining population.[148]

The other difference between "the ADM" and "an ADM" is that there is room for interference in the latter. In criterion (iii) of being the ADM for an effect in a population, it was said that the causal relationship between X and Y should be invariant with respect to other actually varying variables. For an ADM, this is not necessary. For some causal factor to be an ADM, the causal relation between X and Y should be invariant only for some set of values for other variables. For instance, in the factory example above, fuse box explosion is an ADM for factory fires only when the fire extinguishing system is functional, which actually varies in the population of comparison.

With the ADM concept, Waters tries to achieve two things at once: Objectively justifying one kind of causal statement and opposing the parity thesis. Against the philosophical consensus that singling out causes in complex situations is just a pragmatic matter, he offers a stronger, ontological justification for choosing a

[148] This point is extremely important in candidate gene studies. Candidate genes are usually detected in family based methods. It is possible that carrying two mutant alleles at the same locus can be the sole cause of breast cancer in a family. It is "the actual difference maker" in that family. But it is just "an actual difference maker" with respect to a more inclusive population of individuals if that mutation is not present but the effect is.

particular cause among many. According to Waters, once the population and effect are specified, the cause-effect relationship is ontologically fixed. Not everything in a given population actually varies and not every variation in the values of causal variables influences the chosen effect variable. For Waters, a cause is merely a potential difference maker. A potential difference maker is a variable for which there are possible interventions that would change the effect variable. But there should be actual variation in a variable for it to be an ADM.

Against the parity thesis, Waters claims that DNA is an actual and *specific* difference maker whereas other factors such as RNA polymerase either don't vary or their variation doesn't bring about specific changes in the effect variable. Here, it is important to pay attention to the fact that Waters' counterargument is not a refutation of all kinds of parity arguments. He limits his discussion into RNA synthesis and specifically to the determination of RNA sequence. In that domain, there is a further distinction between prokaryotic protein synthesis and eukaryotic protein synthesis. In the case of prokaryotes, DNA specifies the nucleic acid sequence of an RNA sequence letter by letter. RNA Polymerase in bacteria doesn't vary much, and even when it varies, the variation does not act as specific as DNA nucleotide sequence variation. Variation in RNA polymerase can stop RNA and protein synthesis altogether but it cannot determine the sequence of nucleotides in the RNA. The same point can be made for the whole protein synthesis machinery in bacteria. There may have evolved different code scripts in evolution, but possible differences don't put a nearly universal causal factor (e.g. RNA polymerase or the genetic code) on a par with actually varying DNA nucleotide sequences. Thus, it might be said that DNA sequence is the actual specific difference maker with regards to the RNAs a population of bacteria produces.

In eukaryotic RNA and protein synthesis, the mechanism is more complicated. DNA sequence is not directly translated into RNA sequence. In eukaryotes, functional (i.e. transcribed into RNA) parts of DNA (exons) reside between long stretches of nonfunctional (i.e. not transcribed) DNA. RNA synthesis produces different

combinations of transcripts from the same gene, according to the presence of tissue specific factors and the resultant RNA is further modified. Thus, it is possible to create different RNAs or proteins from the same DNA sequence. In this case, Waters claims that DNA sequence is *an actual difference maker* because DNA sequence alone cannot specifically determine the effect variable (i.e. RNA sequence) but it is still the most specific ADM in the population with regards to the effect variable – the set of proteins produced (Ibid.p. 575, footnote #26).

Waters' thesis is correct in its specified domain of application. For higher level phenotypes and of interacting causes, the conceptual victory seems suspect.

7.6 Actual Difference Making and Higher Level Phenotypes

Waters made the right choice in confining his argument to the simplest/clearest cases of Mendelian genetics and to the set of RNA sequences. Because if he had expanded the ADM conception to the genetic causes of more complex effects and to variation in natural populations, all of his criteria would be in jeopardy. In the level of higher, complex phenotypes, interaction and multidimensional variation diminishes the usefulness of the ADM concept.

In Waters' conceptual framework, causes are potential difference makers with respect to an effect. An actual difference making cause is a causal variable whose actual variation causes actual differences in the effect variable. But the difference making capacity of a causal factor might be contingent on the state of other factors. These states, in which a causal factor is an ADM (i.e. it makes a difference systematically), constitute the invariance space of the causal relation. The invariance space is a sophisticated reformulation of the old idea of background conditions. In the case of complex phenotypes and in natural populations, the distinction between ADMs and background conditions is blurred.

The difficulty is in part practical. Individuals in a natural population actually vary in many respects. Their genomes, the temporal sequence of environments they are exposed to vary. Because of this, it is practically difficult to find out which factor

makes the difference in the effect variable. Statistical techniques such as ANOVA are used to overcome this.

The theoretical difficulty originates from interaction. If causal factors such as allelic variation and environmental variation show their difference making capacities *only* when they act together, a conceptual problem arises. There are two possible ways to express the causal relation here:

i) Allelic variation is an ADM whereas the state of the environment constitutes the invariance space in which the causal relation holds; vice versa.

ii) None of the factors are ADMs; only their interaction is an ADM.

In the first statement, one of the interacting variables is held constant; it is transformed into a background condition. But there is a symmetrical relation such that the other factor could also be held constant. The choice of ADM and background conditions is arbitrary. The situation is a clear-cut case of parity. For this reason, the second statement is more reasonable.[149]

In more realistic cases, the factors have both main effects and interaction effects. A good case is Caspi et al's (2003) study on the interaction between genetic variation in serotonin transporter gene's (i.e. 5-HTT gene) promoter regions and stressful life events. This gene was chosen because its product is the target of serotonin reuptake inhibiting drugs – a popular class of antidepressants (Tabery 2014). There are two forms of the promoter region: short (*s*) and long (*l*). A person can have one of the three genotypes with respect to this region: *l/l*, *s/l* and *s/s*. Those who are *s/s* or *s/l* produce the transporter protein with 1/2 efficiency compared to *l/l* genotype. They also show increased amygdala activity upon exposure to frightening stimuli. They have smaller amygdala and cingulate cortex.

[149] This case is identical to the crossing NoRs with no main effects, mentioned in the previous chapter.

People with *s/s* and *s/l* genotypes are more prone to major depression than people with *l/l* genotypes if they experience stressful life events. Stressful life events cause depression in all three types of genotypes, so they are independent ADMs with respect to major depression, whose effects are modulated by the structure of the promoter. The short promoter variant makes a difference only if it is coupled with stressful life events. It is a dependent ADM with respect to major depression.

The short variant of the promoter can be an independent ADM with respect to a deeper phenotype than the symptoms of major depression (endophenotype). I'll give two examples. First one is already mentioned. The efficiency in the production of 5-HTT protein is a biochemical phenotype for which sequence variation is an independent ADM.[150] However, the biochemical phenotype is far away from clinical symptoms of major depression. Moffitt and Caspi (2010) offer a midlevel endophenotype: negative affectivity (Tabery 2014, 140). Negative affectivity is the cognitive-emotional disposition to treat external stimuli more negatively (i.e. as a threat) and to be more sensitive to negative clues than positive ones. People with the short form of the promoter have this dispositional property regardless of their stressful-traumatic experiences; but this disposition shows up as the clinical symptoms of major depression only if they experience such events. Here, the promoter form is an independent ADM with respect to negative affectivity. But it is a dependent ADM with respect to clinical depression.

The serotonin transporter example shows how interaction can be captured in a traditional factorial theory of causation. Moffitt and Caspi's solution (i.e. negative affectivity) reveals an important point about scientific practice. Even when biologists search for interactions, they don't prefer to blur the distinction between interacting causes. In DST, especially in Lewontin's dialectical biology and Oyama's constructive interactionism, identifying something as a cause always depends on the context of explanation. For instance, Lewontin (2000) claims that gene variants show

[150] Certainly, we are assuming that no other actually varying factor affects this difference.

their effects only in conjunction with the total genetic background and the environment. Thus, when a certain phenotypic difference is explained by an allele substitution, the substitution is a cause only in the conditions of the experimental population. But practitioners of science can't postpone their research until an all-encompassing explanatory scheme arises. Moffitt and Caspi didn't offer a general, holistic explanation for their findings. Their explanation was very similar to a model of disease susceptibility (Tabery 2014). Susceptibility is a phenotype that is independent of whether the disease occurs or not. It is a standing disposition caused totally by genes. But the disease occurs only if the susceptible individuals encounter the pathogen. In the case of depression, stressful life events are the pathogens and 5-HTT promoter variants determine the susceptibility/resistance of individuals. Susceptibility/resistance is an *intrinsic* property of genotypes which is *revealed* under some conditions. This perspective has nothing to do with the strong relativism of DST theorists.

Two conclusions follow from this exercise of thought. First is that ADM concept loses its force against the parity thesis when applied to higher levels of phenotype, because of the practical and theoretical difficulties it encounters. Thus, it might be said that parity thesis concerning these levels is secure from Waters' attack.

If Waters' original conception is revised in the manner Tabery (2014) offers, it will be a good tool to capture what gene-environment interaction means for most practitioners of genetics. Tabery calls this revised conception "interdependent actual difference makers". An interdependent actual difference maker is a causal variable which becomes an ADM only in conjunction with another ADM. But as we've seen from Moffitt and Caspi's genetic susceptibility model of interaction, interdependence relation is valid only at the clinical symptom level. At the level of endophenotypes, gene variants have context-independent, intrinsically defined effects. So, our second conclusion is that interdependent ADM concept only captures this traditional, factorial kind of interaction. This is because interdependence is conceptualized as reciprocal *moderation* of the effects of causal variables. Moderation presupposes that

the interactants have independent effects. Stronger forms of interaction – constructive interaction (Oyama), "interpenetration" (Lewontin) – are not popular accounts except for developmental scientists.

7.7 Actual Variation, Difference Making and Standards of Biological Explanation

According to Waters, biologists focus on actual variation rather than potential variation. They are happy with causal generalities limited to actual populations. Although his opposition to the parity thesis is limited to protein synthesis, his diagnosis about biologists imply that he has stronger ambitions than that. The thesis that actual variation is more important than potential variation is a common defense of behavioral geneticists and their followers against the interactionists (i.e. DST theorists). So, ADM is not merely a technical device to capture the primacy of DNA in a very limited context. It is also a general philosophical defense of the variation partitioning approaches against mechanism elucidating approaches.[151]

One point must be made clear. Waters already accepts that in experimental biology, researchers are not confined by actual variation. His point is merely an attack on unqualified versions of the thesis that all causes – potential difference makers – are on a par in causal explanations in biology. This unqualified parity thesis implies that we should take into account all possible sources of variation in order to understand the causes of an event. For instance, the defender of such a radical thesis will say that if we want to understand the mechanism of early embryogenesis, we should expose the embryo to all sorts of possible environments such as 1500 centigrade temperature, a brand new toxin, etc. Since there is no philosopher or biologist who defends such a

[151] This distinction is made by James Tabery (2014). Variation partitioning approaches refer to population level, nonexperimental studies that partition variance into its genetic and environmental components. Mechanism elucidation approaches refer to experimental studies of phenogenesis (i.e. phenotype formation) such as Sydney Brenner's studies on *C. elegans* development.

view, we must interpret his thesis as if it is directed against an actual school of thought, represented by Hogben, Lewontin, DST, etc.

There are two broad approaches to gene-environment interaction. Interaction can be considered as a deviation from an additive model of main effects of causal variables, as Fisher did (Tabery 2014). Or it can be considered as a distinct source of variation apart from the main effects, as Hogben did (Ibid.). These differing perspectives have important consequences in the interpretation of empirical data. In the first formulation, interaction is seen as a rare and usually weak cause of variation.[152] In the second, it is an entry point into the mechanisms of development.

Those who prefer the first formulation also prefer actual variation over possible variation, as Waters does. For instance, in a textbook of behavior genetics it is said that "Although it is useful to think about what could be, it is important to begin with what is – the genetic and environmental sources of variance in existing populations." (Plomin et al. 2008, p. 87). We have seen the drawbacks of this approach in heritability debates. The most important one is that this approach allows for only population-specific causal knowledge. But if the causal relation is essentially population dependent – the causes (e.g. gene variants) are contingent upon the state of a certain population at a certain time – it is difficult to generalize this knowledge. Waters claims that this is not a serious problem for biologists because biologists are satisfied with generalizations that don't hold over a wide range of conditions, as physicists seek (2007, p. 577). But even within biology, this perspective is not shared.

Those who want a deeper understanding of how different phenotypes come to be (Lewontin 1974, Hogben 1933) wouldn't be satisfied with the approach shared by Waters (2007), Plomin et al (2008), and Sesardic (2005). In other words, actual

[152] There is a bias in evaluating the evidence for interaction as reported in Tabery (2014). According to Tabery, even metaanalysis can't overcome this bias.

variation in actual populations won't satisfy the explanatory criteria of some biologists.

A very general problem with the "actual variation in actual populations" approach concerns the causal status of invariant developmental factors. For instance, humans are 99.9% identical with respect to their genomes. Heritability of conserved genomic regions is nearly zero: they don't contribute to population level variance values.[153] But these invariant and conserved regions are where functional DNA (e.g. protein and RNA coding regions) resides. If biologists had confined all of their efforts for actual variation, these regions wouldn't be within their area of interest. The school of induced mutagenesis shows that biologists make possible variation actual in order to investigate mechanisms. They go beyond actual variation. And more importantly, these regions are more important in causal analysis than the regions that vary. The idea of a genetic program and the primacy of genes in development are based on the information carried in these regions. Genetic causation can't be confined to the difference making capacity of actually varying DNA regions, even if one accepts the gene centric perspective. Difference making is not the only form of causal relation genes are involved in.

"Actual variation in actual populations" approach can't be defended as a theoretical necessity. But it is a practical necessity in human behavior genetics. As told in the previous chapter, traditional behavior genetics lacked the experimental tools necessary for identifying the causal mechanisms producing behavior. Behavior genetics is not an experimental science and it relies heavily on statistical tools to analyze variation at the population level. The causes of the population level variation were given a very crude and simplified interpretation: Total variation is an additive function of genetic and environmental variation. The linear model expressed in ANOVA has been taken as a genuine analysis of causes (Lewontin 1974).

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[153] There is variation in coding DNA but it is rarer and it has harmful effects. Thus, this type of variation doesn't contribute much to the heritabilities of those phenotypic traits.

Modern behavior genetics is not limited to this crude biometrical analysis of variance. Genomics provides a dearth of data that could be associated with behavior, or any other kind of complex phenotype. But building causal models out of this data is much more difficult than simply pointing to genetic differences that make a difference. The additive polygenic model is no better than the single gene models of Mendelian genetics. A developmental model of trait etiology is needed and no matter how deep one probes DNA sequence data, this need will not disappear.

The discussion about the importance of heritability, reaction norms and actual variation is a discussion about the standards of explanation. One camp, represented by behavior geneticists and their philosophical followers (Sesardic 2005, Waters 2007) claimed that actual variation in actual populations is all we can begin with. The other camp represented by molecular biologists (Noble 2008), evolutionary geneticists (Lewontin 1974;2000;2001) and developmentalists (Lehrman 2001,Oyama 2000) insisted that a more powerful theoretical framework was needed. This more powerful framework would explain differences by means of explaining the development of individuals:

> Throughout the history of modern biology there has been a confusion between two basic questions about organisms: the problem of the origin of differences and the problem of the origin of state. At first sight these seem to be the same question, and taken in the right direction, they are. After all, if we could explain why each particular organism has its particular form, then we would have explained, *pari passu*, the differences between them. But the reverse is not true. (Lewontin 2000, ix).

The other camp relied on differences:

> Other than at the molecular level, where one gene is seen directly to produce one protein chain, geneticists never deal with units of phenotype as such. Rather, they always deal with differences....
>
> ....It follows from the fact that geneticists are always concerned with phenotypic *differences* that we need not be afraid of postulating genes with indefinitely complex phenotypic effects and with phenotypic effects that show themselves only in highly complex developmental conditions. (Dawkins 1982, pp. 21-22).

The difference-making concept of genetic causation is not a matter of philosophical choice. It was a practical necessity In Mendelian genetics. The gene itself is defined by its difference making capacity. The differences should be visible at the phenotypic level. This causal model is not applicable to complex phenotypes and researchers resort to polygenic models. Polygenic models share one property with Mendelian models: difference making. In polygenic models, gene variants are important in so far as they show a significant statistical association with phenotypic variation (e.g. case vs. control).

If genes were only difference making causes, the idea of genetic program would be meaningless. Genes would be irrelevant in the explanation of common, invariant properties of the members of a species. Genes would not provide "the explanation of why we are human beings, not monkeys" (Watson 1992a).[154] Rather, they would explain why some of us have penicillin allergy and some of us don't.

The difference between these two concepts of genetic causation can best be exemplified by two actual research programs: Evolutionary Psychology and Behavior Genetics.

7.8 Genome as a Program and Genes as Difference Makers: Evolutionary Psychology and Behavioral Genetics

Genetic basis of human behavior was – and still is – the hotspot in the discussion concerning gene centrism. Human behavioral traits are obviously related to genes. But what is the relation between genes and human behavior? Conceptually, genes can be invoked either in explaining universal properties of species or differences between individuals. The conceptual distinction depends on the division of labor between research programs. Plomin et al. (2003) describe the situation, with respect to

[154] In fact, Watson's phrase is also about difference making but at a totally different level than what we have been discussing so far. Interspecies diversity certainly depends on genetic differences. But the question "why we are humans rather than chimpanzees" requires much more than citing such and such variants. The organization of the whole genomes, not single gene variants, could be explanatory here.

behavior genetics and induced mutagenesis school, like this:

> Research in behavioral genetics has focused on within-species interindividual differences, for example why some children have reading disabilities and others do not. In contrast, many areas of psychology and neuroscience seldom mention individual differences and concentrate instead on species-universal or species-typical (normative) phenomena….Until now, genetics has entered neuroscience primarily in relation to gene targeting in mice in which mutations are induced that interfere with normal brain processes…. This approach tends to treat all members of the species as if they were genetically the same except for a few rogue mutations that disrupt normal processes (pp. 4-5)

The same distinction can be made between evolutionary psychology and behavior genetics. Evolutionary psychology is an approach that deals with the evolution of species-typical cognitive structures of humans. The fundamental thesis of EP is that human mind consists of cognitive adaptations. An adaptation is defined as:

> Inherited and reliably developing characteristics that came into existence through natural selection because they helped to solve problems of survival or reproduction better than alternative designs existing in the population during the period of their evolution; example: umbilical cord. (Buss 2014, p. 38).

These cognitive adaptations are like computer programs that solve specific problems encountered by our hunter-gatherer ancestors. The so called adaptive problems include finding food (foraging), constructing tools, finding mates, detecting infidelity, etc. These cognitive programs are genetically determined in the sense that:

1) They reliably show up in almost every organism that develops in a *normal* environment.
2) Their basis of inheritance resides in DNA because only DNA – opposed to epigenetic inheritance mechanisms – can be a reliable replicator for millions of years (Dawkins 1976).
3) Environmental variation can lead to different overt behaviors but the essential features of the programs are not influenced by the environment – unless the environment is extreme enough to divert the development from its normal course. Just like the umbilical cord, the specific values taken by the essential

variables (e.g. the length, width or functionality of the cord) are not predetermined by the DNA but the presence of those programs and the intrinsic functional relations among them are fixed by the DNA.

4) In general, the specific value of behavioral output is not solely determined by the genes but the computed abstract function is solely determined by the genes. In other words, the universal capacity to solve a particular problem is coded in the genes but the specific solution is not coded. For instance, the universal capacity to form calluses is in the genes but whether one develops calluses or how much she/he develops them depends on the genes and the specific environment she/he experiences in her/his life (Buss 2014, 18).
5) In a still higher level of abstraction, environment – including societal customs and hierarchical structures – is the input, behavior is the output and evolutionarily conserved regions of the human genome provide the adapted cognitive structure.

Evolutionary explanations of human behavior are mostly speculative, if they are judged according to the standards of evolutionary genetics. Evolutionary psychology is said to operate at all of these three levels of explanation: Adaptive problem (level 1) ↔ Cognitive program (level 2) ↔ neurophysiological basis (level 3) (Cosmides and Tooby 1997). In order for it to be relevant to the real evolutionary science of human behavior, it should also include a fourth level, namely, the level of evolutionary genetic explanation. An evolutionary genetic explanation requires knowledge of the alternative phenotypes in an ancestral population and the genetic basis of those phenotypic differences. As we saw in the fourth chapter, many simplifying assumptions are made in such explanations. For instance, one can explain the evolution of a complex trait by means of a single locus biallelic model. I don't claim that these models provide the best means of evolutionary explanation, but EP lacks even this simplified form of genetic explanation.

EP so far has only produced explanations at the intersection between level one and two (adaptive problem and cognitive program). Its explanations consist of the identification of universal behavioral patterns (e.g. male's methods of detecting

female infidelity: a cognitive program) and explaining them by means of an evolutionarily reasonable adaptationist explanation (e.g. male fidelity-detection method as a reproductive strategy that is fittest under certain conditions).

EP never delves into neurophysiology or the genetic basis of the reliable development of cognitive structures.[155] Some of the so called human universals are now seen as artefacts of a sampling error.[156] Namely, it is claimed that some universal human behavior patterns such as fairness is a consequence of using a WEIRD (i.e. Western, Educated, Industrialized, Rich, Democratic) sample.

Thus, even if EP is theoretically the most powerful statement of gene centrism, but the lack of empirical evidence at the level of neurobiology and genetics weakens its position for being the fundamental theory justifying gene centric perspective in psychology.[157]

Behavioral genetics is more secure, scientifically (i.e. empirically) speaking. BG is a field of genetics that applies genetic methods to human behavioral *variation*.[158]BG is

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[155] Evolutionary psychology is a theory in psychology, not a branch of psychology and not a branch of evolutionary genetics or neuroscience. Thus, evolutionary psychologists are probably justified in borrowing genetic or neuroscientific explanations from the relevant fields and not performing the research themselves. But they are extremely biased in what genetic or neuroscientific data to include in their works. Steven Pinker (2002), for instance, only refers to the studies in which neural development is considered to be innately fixed by the genes.

[156] For a thorough discussion of the dubious universality of some human universals, see Henrich, Heine and Norenzayan 2010. In that work, the authors make a very strong case against the universality claims of some psychological studies. In summary, they demonstrate that psychological research uses western undergraduate students as its sample and this sample lies at one edge of human behavioral variation.

[157] It is theoretically the strongest candidate because if human cultural variation is just a variation on a common, genetically programmed theme, all cultures would be only byproducts of genetically fixed behavioral capacities. Human nature would constrain what humans can do, regardless of the social structure and this human nature would have a common genetic basis in all humans.

[158] BG deals with human genetic variation rather than the genetic basis of human universals and this distinction is very important.

not speculative like EP. But it has its own problems for a different set of reasons. The most important problem for human BG is that it is not an experimental science.

Behavioral genetics is the field of genetics which searches for the genetic bases of individual psychological differences (e.g. dimensions of personality, IQ). The field can further be partitioned into two subfields: quantitative genetics of behavior and molecular genetics of behavior. Behavior genetics research had traditionally depended more on quantitative (statistical) techniques for "partitioning variance" than identifying the molecular genetic bases of behavior (Tabery 2014, p. 99). These two styles of research are not exclusive. Quantitative research shows that a trait is highly heritable and molecular genetic research can identify DNA variants that contribute to this heritability.[159]

Behavior genetics, from Francis Galton's biometric school till the 21st century, has refined its methods and standards. In the wake of the 21st century, it became clear that most behavioral dimensions (e.g. personality, psychological disease, etc.) had a significant genetic component: "The nature-nurture debate is over. The bottom line is that everything is heritable, an outcome that has taken all sides of the nature nurture debate by surprise." (Turkheimer 2000, p. 160)

Here, it is important to remember that being heritable is not equal to being created by the genes alone, being insensitive to environmental effects, etc. It means that variation in every behavioral trait is at least partially genetic. Let me elaborate why this is so. Think of "years of schooling". This social trait is obviously not genetic in the sense that it is in your genes. Years of schooling could not have been coded in your genome by natural selection because public education is a fairly new human invention. But the difference in years of schooling between individuals is influenced by genetic differences. How is this possible? Suppose that years of schooling correlates with, socioeconomic status, social anxiety, etc. Further suppose that variation in some parts

[159] Missing heritability problem, as discussed in the third chapter, is a problem about integrating the findings of these research programs.

of the genome correlate with social anxiety. If this is the case, years of schooling will correlate with those genomic variants. This explains why a certain social-behavioral trait is associated with certain genes in a certain type of society. The same scheme can be generalized for almost every behavioral trait. The reason is that, tentatively speaking, even a purely environmental effect should manifest itself by modulating the expression of certain genes. If there are differences in those genes, their responses will also be different. Being heritable does not imply that the trait can be reduced to the presence of certain gene variants. As a combined measure of all genetic influences, heritability gives a rough, population specific estimate of the contribution of genetic variation to phenotypic variation. But the causal chain from the gene variants to phenotypes is not made clear by this fact. Heritability by itself says nothing about which genes make a difference in the phenotype.

Genomic data was assumed to solve this problem. The reasoning was simple: Heritable human variation would be explained by matching genetic variants with phenotypes. By this way, the crude, biometric concept of heritability would be transformed into reliable causal knowledge. This expectation is clearly expressed in Kandel's speech:

> What will we learn from the genome that might orient us more to see the patient as a person rather than as a disease state? The genome of course provides us with a periodic table of life. It contains the complete list and structure of all genes. But it provides us not simply with an average-expectable genome. It provides each of us with *our own unique genome*. In time, our genome will be a part of our private medical record. As a result, we in academic medicine will collectively have a catalog of *all* the human genetic variations that account for *all the heritable differences between individuals*. (Kandel 2005, 377-378).

The missing heritability problem showed that this is no easy task. One can locate the fault in statistical techniques, resolution of SNP maps, etc. In other words, one can consider this as a technical problem. But at least some people don't. For them, the problem is in the reasoning.

For instance, Turkheimer (2000) expected that genome projects would find genetic variants associated with behavior but he was pessimistic on whether these associations would be replicable and give cumulative knowledge. The reasons were that:

"(a) Behavior emerges out of complex, nonlinear developmental processes, and (b) ethical considerations prevent us from bringing most human developmental processes under experimental control." (p. 161). A result of (a) is that when a rough biometrical measure such as heritability is analyzed into its components, the sum of the components would not add up to the value of that measure. The missing heritability problem is the consequence of the nonlinear interactions between developmental factors and impossibility of experimental control in human genetics (Turkheimer 2012). According to Turkheimer, this is not a technical problem that can be remedied by better statistics. If it was possible to experiment on humans – raising them in controlled environments or raising genetically identical individuals in different environments – it would be possible to point to distinct causes of variation. The heart of the problem is to decompose a summary measure into its distinct components in order to causally explain a complex phenomenon, without the help of experimental techniques. Turkheimer states that this problem is not specific to genetics, it is also a problem in social sciences. The pattern is like this: You are pretty certain that some general and roughly defined causal factor can explain a significant proportion of a phenomenon of interest but when you decompose the measure into its components, you lose explanatory power. Suppose that the phenomenon of interest is childhood delinquency and the broad measure is poverty:

> On the one hand, to the extent the goal is to explain the environmental etiology of something like juvenile delinquency in a general sense, to identify the specific factors that cause delinquency across a broad range of contexts, only the most general, if not platitudinous, explanations can be found: poverty is bad, stable families are good. But if the question then becomes, what is it about poverty that causes delinquency, is it schooling or peer groups or diet or environmental toxins, the missing environment problem asserts itself: it is at once all of these things and none of them. Together, they all add up to the construct we call poverty, which has a demonstrably negative effect; *but one*

> *at a time, their effects are too small, and too dependent on context, to be quantified reliably or added together meaningfully* [emphasis added] (Turkheimer 2012, p. 55).

This problem shows that in interactive systems, causal decomposition will forever be context sensitive. The causal tractability, which was a prime virtue in Mendelian genetics, is being lost. The gene as the difference maker becomes the gene as difference maker in some contexts. And the techniques to overcome context sensitivity – controlled experiments – demolish global interactivity itself in virtue of making single gene effects unambiguous and stronger. Thus we have a dilemma here: Natural variation without causal tractability and tractable variation without global interaction.[160] The solution is to accept a humble view as most practitioners of genetics do: piecemeal and context sensitive causal knowledge is better than nothing and two views can be integrated in actual research. A recent study in schizophrenia genetics provides a good illustration of the latter point.

In 2014, the Schizophrenia Genetics Consortium published the results of a genome wide association study in which they identified 108 common nucleotide variants (SNPs) that were significantly correlated with schizophrenia. Some of these SNPs resided in the vicinity of genes coding immune system related proteins including major histocompatibility complex proteins. The link between immune system functioning and schizophrenia was already suspected before the study and the findings reinforced that idea. In 2016, a team of researchers picked out the Complement Component 4 (C4) gene and further analyzed its functioning in brain development (Sekar et al. 2016). C4 gene has two versions: C4A and C4B. In previous studies, C4A had been implicated in synapse pruning (i.e. elimination) in the central nervous system. Synapse elimination in the association cortex is an important component of brain maturation and it continues "from adolescence to the third decade of life" (Ibid.). In schizophrenia patients, this process is abnormal and

[160] Neven Sesardic (2005) summarizes this realistic viewpoint with these words: "A good slogan for many biological contexts would be: observe locally, think causally (and forget 'globally')" (p. 83).

the onset of schizophrenia coincides with the period when synapse elimination is most extensive – late adolescence and early adulthood. There seems to be a functional connection here. The researchers found that there was a 1.4 fold increase in C4A expression in schizophrenia patients' brains. In addition, they used a mouse model to verify the functional connection. They showed that mice homozygous for the nonfunctional C4 showed less than normal pruning, wild type homozygotes had normal pruning and heterozygotes lied in between.

The study does not provide a conclusive evidence for the feasibility of integration of association studies with experimental studies, for a handful of reasons. One important point that needs clarification is whether there is a cognitive phenotype that is analogous to schizophrenia in mice. But the study at least shows that at a lower level of phenotype (synaptic pruning), some meaningful similarities can be found. This is enough to continue research, even if the results of individual studies would always be suspect. The results satisfy the humble view that knowledge is gained in a piecemeal fashion. It also shows that integration of GWAS findings and stronger experimental methods is possible in practice.

Both evolutionary psychology and human behavior genetics traditionally rested on a top-down approach. Genes are shadows of their corresponding phenotypes, whether these phenotypes are species-typical traits or interindividual differences. But when we look from the bottom – the molecular level – a different picture emerges. Molecular gene is quite different from the Mendelian gene because it is defined by a quite different causal role.

7.9 Genes from the Top and Genes from the Bottom

In early Mendelian genetics, genes were abstract entities residing on chromosomes like beads on a string and whose locations are detected by linkage analysis. They are known through their effects. More correctly, they are examined through the effects of their variant forms and the strength of the linkage between these variants and markers.

Mendelian gene is a statistical abstraction that explains inheritance of certain forms. Suppose that in a haploid organisms, there are three versions of a gene – alleles – that show strong correlation with flower colors such as yellow, red and white. Alleles don't determine alternative flower colors. But in organisms with different alleles, the cause of phenotypic differences is allelic differences, given that all other relevant factors (e.g. alleles at other loci, environment) are invariant. Thus, the Mendelian gene explains the phenotypic differences in a population of organisms, rather than the phenotype *per se*. In this approach, the difference making capacity of alleles may be abbreviated in phrases like "gene for redness", “gene for whiteness" but these are only abbreviations.

For molecular biology, a gene is a piece of DNA that acts as a template in protein synthesis. This definition also depends on an effect of genes. In Mendelian genetics, phenotypic differences were definitive for genes and in molecular biology, the causal role in protein synthesis is definitive of genehood. Still, there is an important difference. In the case of molecular genes, there is a much more direct connection between structure and function. The function of a molecular gene as a sequence of nucleic acids is to determine the amino acid sequence of polypeptides. This is the "gene as transcribed code" (Gerstein et al. 2007).

In this old molecular gene concept, genes are taken to be continuous nucleotide sequences with a one to one relation to protein sequences. But in eukaryotes, protein coding sequences are dispersed between noncoding regions. Alternative splicing produces many proteins out of this set. According to an estimate, an average of 5.4 protein isoforms corresponds to a single gene. So, the gene is still defined as a template for protein synthesis but out of this template, more than one kind of protein can be synthesized. One-to-one relation between genes and proteins is not a definitive feature of the eukaryotic gene.

Alternative splicing is just one part of the complexity of the eukaryotic genome. Post-transcriptional modifications, synthesis of noncoding RNAs, their regulatory

functions, diversity in the mechanisms of regulation, make it impossible to equate the Mendelian gene with the molecular gene.[161]

One of the interesting results of the HGP, as mentioned above, is that human genome consisted of 30000 genes. This estimate was later reduced to 21000. The number of genes DNA regions that are either known to code for proteins or which show sufficient structural similarity to known genes. The reason that this numbers are interesting is that they look too small to be able to account for the complexity of humans. But this number by itself doesn't mean so much because the complexity and interactivity of gene networks can produce this complexity. Besides, defining genes with respect to their template role in protein synthesis might be a mistake.

Let me elaborate the latter point. Human Genome Project was a project that focused on determining the total sequence rather than the functional organization of the genome. A following project – Encyclopedia of DNA Elements (ENCODE) – was aimed at analyzing the 1% portion of this sequence according to functional criteria such as the effects of stabilizing selection, RNA and protein synthesis, chromatin accessibility, etc. The report of the project was published in 2007. The results can be summarized such that (ENCODE Project Consortium 2007):

A significant portion of DNA is transcribed. The noncoding regions show significant overlap with coding regions. In other words, the same region is used as a template in both protein synthesis and the synthesis of noncoding RNAs. Regulatory sites – the sites where transcription factors bind – are symmetric: they can occur in the downstream or upstream of the transcribed regions. Many regulatory regions are nonfunctional, their functionality depend on chromatin accessibility. Some of the evolutionarily conserved regions – selectively retained regions – have no apparent function. Researcher believe that these sites probably have unknown functions. In

[161] According to Pearson (2006), a study in Japan found that 63% of the mouse DNA is transcribed despite the fact that only 1-2% of it contains exons. If these noncoding RNAs have a function, the number of genes will be revised accordingly.

contrast to the conserved but nonfunctional regions, there are functional but nonconserved regions.

ENCODE project showed that transcription in human genome is much higher than expected. But the function of these transcripts is still not certain. Some kinds of nontranslated RNA were already known to be functional. Ribosomal RNA was known to be a structural element in the formation of ribosomes and micro RNAs were known to regulate transcription. But the RNA transcripts discovered in the ENCODE project weren't assigned clear functionality, at least in 2007.

ENCODE Project Consortium didn't offer a revised definition of the gene concept. Rather, they offered a revision in our models of transcription and of the genome:

> Our analyses of numerous orthogonal data sets firmly establish the presence of these transcripts, and thus the simple view of the genome as having a defined set of isolated loci transcribed independently does not seem to be accurate. Perhaps the genome encodes a network of transcripts, many of which are linked to protein-coding transcripts and to the majority of which we cannot (yet) assign a biological role. Our perspective of transcription and genes may have to evolve and also poses some interesting mechanistic questions. For example, how are splicing signals coordinated and used when there are so many overlapping primary transcripts? (Ibid. 812-813).

Despite the fact that no new and explicit definition of genes is offered here, it is certain that new gene concepts will not be limited to the coding role in protein synthesis. Even the molecular gene is dependent on some molecular phenotype beyond polypeptide sequence. It is important to keep in mind that the limits of the molecular phenotype determine the limits of our molecular gene concepts. New gene definitions are aimed at capturing this dimension of genetic causality with different levels of permittivity. For instance, in a new and relatively conservative definition of genes, it is said that "The gene is a union of genomic sequences encoding a coherent set of potentially overlapping functional products" (Gerstein et al. 2007, 677). The definition is conservative because regulatory regions and regions that code for nonfunctional RNAs are left out of its limits. And it is conservative because it defines genehood with the template role in RNA synthesis. But in this definition, acting as a

template in noncoding RNA synthesis also becomes a definitive feature. Thus, we might expect that the number of genes will increase with this definition, if those RNAs have biological functions.

The "coherence" criterion means that the template role in the synthesis of end products – protein isoforms, noncoding RNAs – unites a set of exons. In other words, exons which overlap on the DNA but are used in the production of independent proteins or RNAs don't constitute a gene. The set need not share an exon that is common to all end products. The case might be schematized as such:

Suppose A, B, C and D are polypeptide domains synthesized from corresponding exons a, b, c and d. If the protein set consists of A-B, B-C, A-C, and A-D, the set is coherent and there is only one gene. If the set consists of A-B and C-D, the set is not coherent and there are two genes. A similar scenario can be constructed for functional RNA transcripts.

A more permissive definition is given by Eva Neumann-Held (2001). Neumann-Held's definition of a gene includes any causal factor that has a role in protein synthesis. This is an ambitious attempt at redefining the gene in accordance with the parity thesis. According to her process molecular gene (PMG) concept:

> "Gene" is the process (i.e. the course of events) that binds together DNA and all other relevant non-DNA entities in the production of a particular polypeptide. The term *gene* in this sense stands for processes which are specified by (1) specific interactions between specific DNA segments and specific non-DNA located entities, (2) specific processing mechanisms of resulting mRNA's in interactions with additional non-DNA located entities. These processes, in their specific temporal order, result (3) in the synthesis of a specific polypeptide. This gene concept is relational, and it always includes interactions between DNA and its (developmental) environment. (Neumann-Held 2001).

This definition is too permissive because it includes any factor that interacts with the protein synthesis process. The difference between DNA as a template and other factors as interactants is lost. And worse still, it is practically impossible to categorize genes according to this definition. For the definition includes every context-

dependent interaction. The gene concept was useful for its simplicity, both in Mendelian genetics and early molecular biology. PMG complicates rather than simplifies and it doesn't refer to some robust natural unit, so it is practically useless and metaphysically burdensome.

A more sensitive approach to genes is developed by Lenny Moss (2001, 2003). Moss offers two gene definitions to capture two distinct explanatory roles genes play in biology. The first is Gene-P, the preformationist gene concept. It is the difference-making, Mendelian gene used in medical genetics. Preformationism here shouldn't be taken literally. Think of the gene for blue eyes. It doesn't code for blue eyes in any reasonable meaning of the term "coding". It is the lack of a normal sequence and the phenotype is the response of the remaining genes to this loss. But Gene-P is an almost certain predictor of the phenotype such that we might act "as if" it codes for blue eyes. This "as if" preformationist meaning captures the use of "gene for X" locution in medical genetics. The topdown (i.e. gene as a marker for phenotypic differences) approach is apparent in this definition.

Moss' bottom-up gene concept is the gene as developmental resource (Gene-D). In this definition, a gene is defined by its nucleotide sequence and its effects on higher level phenotypes are indeterminate (Moss 2001). A Gene-D is defined by its template resource function "in the production of various 'gene-products' – directly in the synthesis of RNA, and indirectly in the synthesis of a host of related polypeptides" (Ibid, p. 88). For instance, the complement C4 gene is a template resource from which different proteins are synthesized. An excess expression of the C4A isoform is associated with schizophrenia via the intermediate phenotype of synapse pruning. But the gene itself is not a gene for schizophrenia because the proteins synthesized from that region act in many biological functions. Only when it is expressed excessively in the context of brain development, it makes a specific difference.

Genes in this developmental conception don't carry information in the programming sense of the term. Their connection to a specific phenotype is mediated by the

products and activity levels of many other genes. And the latter are determined by the overall state of the cell and its surrounding.

Genes in this concept still carry information. But only the "information as data" or "information as template resource" concept is applicable here. Genes are not considered as molecular homunculi which direct phenogenesis. Genes are tools used by the organism, not the other way around. Specific sequences act more like "pieces of re-usable lego" (Noble 2008, 3010).

7.10 Conclusion: What is Left of the Gene Centric Perspective?

The gene centric perspective, from early Mendelian genetics to the HGP, attributed a diverse array of causal powers to genes. Similarities as well as differences were in the genes. Genes provided the blueprint whereas nongenetic factors were mere building blocks. Genes were the ultimate units of selection. Genes carried information in many senses of the term. If we could understand the DNA text, we would be able to discover the deep, real causes of disease. HGP and following studies produced a haystack of annotated data. GWA studies implicated SNP variants associated with disease. But this data didn't provide straightforward functional knowledge about disease and health. Gene as the unit of functional specificity was transformed into gene as template resource gaining functional specificity in a system of interactions. Even if one believes in the primacy of genes in biological explanation, the meaning of DNA and gene expression data is determined by their connections to what happens in specific cell types and tissues. Sydney Brenner, in his Nobel Lecture, suggested focusing on cell types rather than genes *per se*:

> We are all conscious today that we are drowning in a sea of data and starving for knowledge. The biological sciences have exploded, largely through our unprecedented power to accumulate descriptive facts. How to understanding genomes and how to use them is going to be a central task of our research for the future. We need to turn data into knowledge and we need a framework to do it. *So genocentric has modern biology become that we have forgotten that the real units of function and structure in an organism are cells and not genes* [emphasis added]....

> Not only is the cell the only physical locus for gene action but it is the correct level of abstraction to construct a framework for understanding functions. (Brenner 2002).

Genes as specific difference makers became more and more dependent on context. The unambiguous differences associated with gene substitutions observed in classical genetics now seem to be just the tip of the iceberg. Drastic mutations were the only tools available in classical genetics that could be used to uncover the normal functioning of a gene. But molecular cell biology changed the picture very much. As we have seen in new gene concepts, gene as a molecular template resource has a very indirect connection to observable phenotypes. When a causal connection has many mediating steps, those steps become as explanatory as the so called cause itself. Kenneth Waters' specific actual difference making concept is applicable in a very limited version of the parity thesis, exactly for this reason.

Informational concepts have been used to support the primacy of genes. No formal theory of information was offered. There are many senses in which DNA can be considered as an information bearer. The weakest sense is which sees DNA as a data source. The strongest is the one in which DNA is taken to bear the genetic program. The programming idea has been stated to capture the regularities in development. It was also tied to the idea that natural selection "designs" the genome. Thus, the programming idea is about the essential properties of a species. The idea of a genetic program is both two deterministic and too indeterminate at the same time. When it is understood like a prototypical computer program with strict instructions, it implies genetic determinism. But there seems to be no explicit instructions in the genome. In other words, the genome is not neatly divided into routines, subroutines, etc. The post-ENCODE view of genetic program is much looser than what happens in a serial computer:

> Rather, threads of execution are intertwined in a rather 'higgledy-piggledy' fashion, very much like what would be described as a sloppy, unstructured computer program code with lots of GOTO statements zipping in and out of loops and other constructs. (Gerstein et. al 2007. p. 675).

Calling this massively parallel coordination of biochemical events "the execution of a program" is what indeterminacy amounts to. Such a flexible concept of program can be applied to any kind of regular process, so, the program analogy becomes less and less definitive. It becomes a scaffolding term that loosely connects our knowledge about the mechanisms of gene expression. It creates the illusion of theory based unity where there are only mechanisms and their time dependent interactions.

DST theorists have proposed the parity thesis in order to oppose an ungrounded form of gene centrism. But there is still a privileged role for DNA, even after these sustained attacks. Some of the reasons concern the special role of DNA based inheritance in evolution and some concern the practical merits of DNA sequence data:

1) DNA based inheritance is much more reliable than other, epigenetic forms of inheritance. The timeframe in which evolution occurs makes DNA based inheritance the most remarkable candidate for tracking evolutionary changes. This reliability depends on the DNA repair mechanism. The fact that there is such a *dedicated* mechanisms shows that DNA based inheritance is really special for organisms. There is no point in papering this fact under the cracks, as some proponents of DST do. The correct stance is to see that in the absence of DNA, even the protein synthesis machinery will disappear in a handful of generations (Lewontin 2001).

2) DNA sequence data gives a static fingerprint of an organism. This fingerprint shouldn't be confused with a "blueprint". DNA sequence data doesn't give a description of the adult organism. But it is still the most robust source of information such that it doesn't change much in the lifetime of an organism. For instance, once DNA is isolated from a patient's blood and sequenced, it becomes an invariant source of information. But proteome or metabolome data doesn't have this lifetime stability. This is why DNA is a special information-as-data source.

3) In eukaryotic genetics, alternative splicing, RNA editing etc. prohibits one to one matchings between DNA and polypeptides. But even under these conditions, DNA sequence is the most specific determinant of polypeptide sequence. More

importantly, there is no clear-cut coding relation other than the one between DNA and proteins.[162]

Given these points, DNA sequence information will continue to perform a central role in biological research, without the burdensome theoretical assumptions such as the genetic program. In biology, mechanisms are more important than grand theories.[163]And the mechanisms of gene expression show only a loose similarity to the working of a program.

[162] A kind of "template" relation is found in membrane synthesis (Moss 2001). But, here templating is very coarse grained, as opposed to the case with DNA.

[163] Theory of Evolution is an exception to this.

CHAPTER 8

CONCLUSION

In this thesis, I did three things. Firstly, I offered a history of genetics and I tracked the concepts of "gene" and "gene action" in different periods and different fields. Secondly, I tried to connect this history to the general philosophy of science issue of scientific progress. Lastly, I offered a critical evaluation of genetic determinism and gene centrism.

The central question was why genes gained so much prominence in biology and related fields. Some biologists have defended gene centrism by means of the concept of information. I criticized this kind of defense because information and the related concept of genetic program lead to two problems. When the program or information metaphor is taken at face value, it leads to the not-so-popular view of genetic determinism. When it is used in a more flexible fashion, it offers no concrete model for development, physiology or evolution. If "genetic information" and related concepts cannot ground the prominence of genetic data in biological research, why did genes become so central?

History of genetics shows that the most fitting role for genes is that they causally track heritable differences between individuals. Causal tracking of differences is the only invariant property of genes in the history of genetics. This does not mean that all genetic changes cause phenotypic differences or that only genetic differences cause phenotypic differences. It only means that genetic research is centered upon the investigation of the effects of genetic variation. Causal tracking is different from mere correlation or bookkeeping in the sense that genes are partial causes of phenotypic differences.

A second conclusion that might be derived from the history of genetics is that the definition of gene is dependent on the phenotypic effects of genes. In Mendelian genetics, the gene was the cause of observable phenotype differences. In molecular genetics, the genes are pieces of DNA that code for proteins. Protein structure is a molecular level phenotype. In evolutionary genetics, a gene is a difference maker with respect to fitness.

A third point is that progress in genetics did not come directly from a grand theory. Here, by theory I mean a set of interrelated proposition which explain phenomena in a specific domain. Mendel's discovery surpassed the theories of its time not because it "explained" better but because it made the phenomena of inheritance an object of experimental inquiry. Progress in genetics came through positive heuristics. The multifactorial theory of inheritance, the sequence hypothesis and central dogma and the idea of metabolic regulation at the genetic level had heuristic value because they simplified the problems, they offered a direction to research and they provided insights about the ways to deal with anomalies.

A fourth conclusion concerns the role of gene concept in evolutionary genetics. The gene in evolutionary genetics was not much different from the Mendelian gene. However, its definitive effect concerns the abstract property of fitness. The gene is a difference maker with respect to fitness. Evolution by natural selection is represented as a gradual fixing of the allele with higher average fitness. The beanbag genetics dispute concerned this simplistic vision of evolution as replacement of one allele by another. These were methodological simplifications that made evolution tractable, but the basics of population genetics indicated, for some thinkers in the field such as G. C. Williams and Richard Dawkins, that the Mendelian gene is the ultimate unit of selection. This was the gene centric vision concerning evolution. I claimed that genes are neither the exclusive units of selection nor mere bookkeepers. They are causal difference makers whereas the most significant unit of selection is the individual organism.

Another important conclusion is that contemporary discussions about genetic determinism cannot be solved by the conceptual tools of modern genetics. In modern debates, genetic determinists don't claim that human behavior is fixed by genes, that behavior is unmodifiable or that a few alleles can explain behavioral variation. The importance of gene-environment interaction is also accepted by everyone in the debate. This is at least the consensus position among thinkers who have been criticized for being genetic determinists and their opponents. Thus, it is difficult to clearly delineate genetic determinists from the opposing camp. However, a subtle form of genetic determinism can still be defined. In this form of genetic determinism, it is assumed that intervention depends on the knowledge of genetics. In other words, genetically determined traits are modifiable but only by means of gene-sensitive techniques. This form of genetic determinism cannot be captured by "the gene for X" conception, heritabilities or norms of reaction.

The debates about genetic determinism gave way to the methodologically oriented issue of gene centrism. Of course, this doesn't mean that gene centrism has been defined as a methodological stance by its defenders or critics. The critics of gene centrism claimed that gene centrism depended on a false theory about the relation between genotypes and phenotypes. This theory depended on the assumption that DNA as a static information source could explain the dynamical process of development. Critics offered a thoroughly interactive system of causation. Even if the critics - namely the DST followers - offered an improved theory of genotype-phenotype relation, it did not have the intended restructuring of biological research around the concept of developmental systems, except perhaps in some departments such as developmental psychology. Gene centrism survived those theoretical criticisms. Why?

My answer is mostly pragmatic and empirical. Gene centrism did not survive for offering the best theoretical framework to understand key biological processes. It survived because DNA is at the center of so many processes and probing DNA is a good starting point in many areas of research. DNA does not give the whole causal

story about these processes but because it is related to almost any biological process and because it is a static source of information, it gained prominence in biology.

In the case of evolution, another dimension is added to the advantages of DNA data. DNA based inheritance is the only dedicated system of inheritance, which is supported by the observation that there is a complex repair mechanism for its reliable replication. This makes DNA a very good "bookkeeping" device. Evolutionary changes can be inferred from changes in DNA sequence and no other information source can provide such valuable knowledge.

The gaps in this thesis study - either the ones in the core chapters or in the connections between them - are suggestive about the ways in which it can be further improved. For instance, my history of genetics begins with Mendel's 1865 paper and ends in 1961. The period between 1961 and the beginning of the Human Genome Project (1990s) were omitted. This period was the period in which the molecular biology of eukaryotic genomes was developed. If this period had been covered, the reason for the inadequacy of the information concept would be more clearly shown.

In chapters 2-4, I mostly used the primary works of high caliber geneticists. Citing only geneticists creates a biased viewpoint concerning the history of biology in general. The emergence of the gene centric vision cannot be explained solely by the success of genetics in the last century. There were other research traditions such as embryology or cytology, and genetics must have interacted with these disciplines. Investigating the mutual impacts between these fields and genetics would provide a more complete historical picture.

In addition, the geneticists and molecular biologists cited were the founders of the field. They had strong interest in theoretical work and this creates another bias. The works cited were mostly reviews written by the theoreticians (e.g. Morgan, Muller, Johannsen, Crick). If the scientists in more practical lines of work such as agronomy, animal breeding or medicine were given a fair hearing, the practical dimension of scientific progress would be better depicted.

Another possible line of future work concerns the specifics of behavioral sciences. The theme of the sixth chapter is genetic determinism, an issue that obviously has social and political dimensions. A comprehensive piece of writing on the topic should have included cultural impacts on human behavior and the validity of building social policies on the ground of genetic knowledge, but I chose not to include them for a handful of reasons. The chief reason is that, the aim in the whole thesis is to uncover the forms of genetic explanation, and how they evolved over time, not the contents or the truth of them. To put it in another way, I am interested in the methodological problems concerning the genetic basis of complex traits, whether they be years of schooling in humans or foraging in Drosophila melanogaster. This equivocation of complex animal traits and human traits leads to troubles that I am aware of. One such trouble is to see some human behaviors such as years of schooling as biological traits at all. It is questionable whether all measurable variation in human behavior corresponds to natural trait categories. It is obvious that years of schooling is not by itself a biological property because schooling itself is not a natural part of our biological endowment. A more subtle problem involves the equivocation of medical abnormalities with normal variation in behavioral traits.

For instance, the sixth chapter represents the issue of genetic determinism as if there is no difference between common diseases and behavioral phenotypes such as IQ. Through the perspective of genetics, genetic architecture of a trait is at the center stage and with respect to genetic architecture, these traits don't differ much. Both trait types involve many genes with small effects and the variation in both types result from the interaction of various environmental factors with those great many gene variants. But, the chapter lacks relevant data on the effects of culture on behavior. If the effects of culture are incorporated into that chapter, a more complete picture of the state of affairs would be given. Or that could show that behavioral variation and common diseases are totally different. They might require different treatments.

In this thesis, I've put much emphasis on the infinitesimal model, which might be interpreted as an acceptance of additive model of gene action. It is a possibility that

missing heritability is best explained by epistasis or gene-environment interactions in the case of humans.

The problem of genetic architecture requires careful examination. It is one possible expression of the relation between genotypes and phenotypes. The "architecture" concept implies a complex structure. But it also implies a deterministic relation between genotypes and the ultimate phenotypic outcomes. As defended in the 6th chapter, the complexity of causal relations between genetic makeups and the phenotypic outcomes is not a counterargument against genetic determination. The missing heritability problem has shown the importance of genetic architecture, for the problem indicated that the genotype/phenotype relation is not a simple matter.

The last chapter can be improved in two lines. The first is that the philosophical literature on information concept could have been covered more fully and evaluated in a deeper fashion. For instance, there are DST followers who have no problem with the concept of information but only criticize the thesis that the genetic material is the exclusive source of biological information. Also, the semantic concept of biological information and its teleological underpinnings could be analyzed more thoroughly. However, I don't believe a better, extended concept of information would contribute much to the progress in biology. Substantive problems such as the control of development cannot be solved by better definitions. The new definition would share the fate of the old one: New mechanisms will be discovered, they will be interpreted in the new informational framework, and that's all. No new knowledge will follow from that.

The second line of improvement concerns the meaning of interaction. In the last chapter, I claimed that strong forms of interaction don't suit the daily work of geneticists and I offered a modest approach that depends more on piecemeal causal knowledge. However, there are models of systems biology which can integrate many causal influences into a holistic system of causation. An investigation of these models can shed light on the problem of interaction. More specifically, they might replace our reductionist and mechanical view of causation with the system level dynamics. If

this is done, the "difference making" concept of genes as well as the "information bearing" concept of genes will lose their significance. Because in such systems, the difference making capacity of gene variants depends on the total state of the system.

Systems biology provides a holistic approach to biological processes. The gene centric perspective, according to this perspective, is inadequate because it attributes the orderly dynamics of a system to the genetic material but the organism is an interactive system composed of many other components besides genes and order – as well as disorder – in biological systems cannot be mapped unto DNA. A central controller located in the DNA would be a nice solution to the problems of development, physiology and evolution. However, the contemporary knowledge and its theoretical expression in systems biology call for a different paradigm.

The system biological view of biology, similar to DST, is different from the traditional gene centric perspective in many respects. For instance, in systems biology, the fundamental phenotypes of organisms are seen as emergent properties rather than the products of explicitly coded instructions. This viewpoint is akin to the epigenetic view of development in which, complexity of the outcome is a result of interactions rather than a preformed plan of development. With respect to the possible improvements for this thesis study, systems biological viewpoint points to the directions how biological research can progress.

One possible direction concerns our understanding of causation, as mentioned in preceding paragraphs. This direction is fundamental because causation in biology will soon become a great conceptual problem, given the inadequacy of the gene centric paradigm. The problem is to map genetic variation onto phenotypes, and it is now obvious that this mapping will not be straightforward. By a straightforward mapping, I mean the ability to point out specific genetic variants which are associated with certain phenotypes in a context independent fashion. Even the "mapping" conception of cause-effect relations needs revision and systems biology provides an opportunity to do so.

If the systems biology perspective is adopted, the linear and clear-cut cause-effect relations will be abandoned. Interactive systems pose many problems for the ordinary conception of cause-effect relations. Such systems represent more causal knowledge than static cause-effect maps.

Such systems can be modeled in systems perspective and they are simulatable, which means that it is possible to manipulate some parameters of such systems in a virtual setting. However, simulation is not experimentation and experimentation is the most robust form of gaining knowledge in biology. Reconciliation between system biological simulations and the experimental paradigm will be a major theoretical problem in biology.

Systems biology offers a truely holistic approach but it is dubious whether most practitioners in this field are bound by the holistic/interactive spirit. As O'malley and Dupré (2005) point out, system biologists are either theory guided or they are pragmatic followers. Many biologists disappointed by the gene centric methods have migrated to systems biology, but this does not mean a change in perspectives. When genomic data is not enough, transcriptome or the metabolome will aid. The theoretical framework is still reductionistic in the sense that these scientists are searching for singular causes for their phenomenon of interest.

Given these points of improvement as future prospects, it is probably the time to summarize what this thesis achieved. This thesis has indicated that the gene centric vision need not be defended on the ground of information concept. The history of genetics showed that genes were conceptualized as difference makers for nearly 50 years after the rediscovery of Mendel's laws. Information concept entered into biology by the 1950s, the founding period of molecular biology. But it was tied strictly to the process of protein synthesis. In a sense, it had a limited domain of applicability. The metaphorical usage of the term, on the other hand, is much more flexible; it could be extended to any domain where genes are causally involved. This metaphorical usage creates the false impression that there is an information based theory behind gene centric research. However, gene centrism prevailed mostly

because of the centrality of DNA in biological processes. DNA is a standing target which acts as a relay station in biological research.

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APPENDIX A

TEZ FOTOKOPİSİ İZİN FORMU

ENSTİTÜ

Fen Bilimleri Enstitüsü	☐
Sosyal Bilimler Enstitüsü	X
Uygulamalı Matematik Enstitüsü	☐
Enformatik Enstitüsü	☐
Deniz Bilimleri Enstitüsü	☐

YAZARIN

Soyadı : Akbay
Adı : Gökhan
Bölümü : Felsefe

TEZİN ADI (İngilizce) : Conceptual Change and Scientific Progress in Genetics

TEZİN TÜRÜ : Yüksek Lisans ☐ Doktora X

1. Tezimin tamamından kaynak gösterilmek şartıyla fotokopi alınabilir. X
2. Tezimin içindekiler sayfası, özet, indeks sayfalarından ve/veya bir bölümünden kaynak gösterilmek şartıyla fotokopi alınabilir. ☐
3. Tezimden bir bir (1) yıl süreyle fotokopi alınamaz. ☐

TEZİN KÜTÜPHANEYE TESLİM TARİHİ:

APPENDIX B

CURRICULUM VITAE

Personal Information

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Research Areas

Philosophy of Science, History and Philosophy of Biology, Philosophy of Mind

Education

2010-2016	PhD (METU Philosophy)
2006-2010	MA (METU Philosophy)
2000-2006	BS (Bilkent University Molecular Biology and Genetics

Foreign Languages

English	Advanced
German	Beginner

MA Thesis

Akbay, G. (May 2010). "Function, Reduction and Normativity".
Supervisor: Prof. Dr. Ayhan Sol.

Publications

Popular/Not-Refereed

Akbay G. (2007), "Bilincin Evrimi". *JMO Haber Bülteni*, 2007/2, s.44-48

Refereed

Sol A. and Akbay G. (2009), "Memory, Personal Identity, and Moral Responsibility", *Analecta Husserliana*, 101(1), p.167-179.

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Akbay G., (Aralık 2013). "Genetik Belirlenimciliğin Tarihi: Morgan'ın Sinek Odasından Genom Analizine", 4. Evrim, Bilim ve Eğitim Sempozyumu. İstanbul, Türkiye

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Translations

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Work Experience

Courses Assisted

Philosophy and Evolution. (Fall 2013)
Scientific Method II. (Spring 2014)

APPENDIX C

TURKISH SUMMARY

Geçtiğimiz yüzyıl genin yüzyılı olarak adlandırılır. Mendel'in kalıtım yasalarını keşfetmesinden insan genomu projesine ve bunu takip eden projelere kadar geçen sürede genetik, biyolojik bilimler içinde merkezi bir yer edindi. Bu çalışmada bu sürecin dönemeçleri, kavramsal değişim ve bilimsel ilerleme açısından değerlendirilmektedir.

Kalıtımın bilimsel bir konu olarak ele alınması Mendel'in 1866'da yayınlanan makalesinden çok önceye dayanır. Kalıtımın bilimsel incelenmesini Hippocrates'e kadar takip etmek mümkündür. Ancak kalıtımın kontrollü deneylerin nesnesi haline gelmesini ve matematiksel genellemelerle ifade edilecek hale getirilmesini Mendel'e borçluyuz. Ayrıca, Mendel'in deneysel yöntemi 20. Yüzyılda başarılı bir araştırma programına dönüşebilmiş bir kalıtım kuramıdır. Bu yüzden Mendel'i, bugün bildiğimiz anlamda genetik biliminin atası sayıyoruz.

Mendel, 9 yıl süren deneylerinin sonuçlarını aktardığı makalesinde kalıtımın kesikli birimleri olduğunu ve bu birimlerin gamet aracılığıyla yavrulara aktarılmasında basit matematiksel yasalara uyduğunu söyler. Mendel'in deneylerinde kalıtımsal bir özelliği belirleyen bir çift faktör bulunur. Mendel'in ilk yasasına göre bu faktörler gamet oluşumu sırasında ayrışırlar ve her gamette faktör çiftinin teki taşınır. Mendel'in ikinci yasasına göre ise farklı kalıtımsal özellikleri belirleyen faktörler birbirlerinden bağımsız olarak aktarılırlar.

Bugün Mendel yasaları olarak bildiğimiz genellemeler, Mendel'in çaprazlama deneylerini yorumlamasını kolaylaştıran birer araçtı. Bu netlikte yasalara ulaşabilmesinin nedenlerinden biri de seçtiği özelliklerin izlediği kalıtım yolunun

basitliğiydi. Ders kitaplarına konu olan sarı-yeşil ve buruşuk-düz özellik çiftleri hem farklı kromozomlar üzerinde bulunuyordu (bu yüzden bağımsız ayrışıyorlardı), hem morfolojik açıdan çok kolayca ayırt edilebiliyorlardı, hem de alternatif faktörler arasında çok net baskınlık-çekiniklik ilişkileri vardı. Model organizmayı doğru seçmiş olmak da birçok avantaj sağlıyordu. Bezelyede döllenme sürecini kontrol altında tutmak mümkündü. Bezelye kendini dölleyen bir bitki olduğu için saf soylar elde etmek kolaydı. Ayrıca bezelyede gamet oluşumu Mendel yasalarını keşfetmek için elverişliydi çünkü yetişkin bitki faktör çiftlerinin ikisini, gamet ise sadece birini taşıyordu. Mendel aynı deneyleri *Hieracium* ile yaptığında beklediğinin tam tersi sonuçlarla karşılaşmıştı çünkü bu bitkide gametler iki faktörü birden taşıyordu. Mendel yasalarına ulaşılmasında model organizma ve özelliklerin seçimi kolaylaştırıcı bir etki yapmıştı.

Mendel'i çağdaşı olan kalıtım kuramcılarından ayıran temel özelliklerden biri de deneylerindeki titizliktir. Mendel deneyleri özet olarak, saf soylar elde edilmesine, bunların birbirleriyle çiftleştirilmesine ve yavrular içindeki özellik dağılımının hesaplanmasından ibarettir. Mendel yasaları bu dağılımdan türetilen genellemelerdir. Mendel meşhur 3:1 baskın/çekinik oranına ulaşabilmek için binlerce bitki kullanmıştı.

Mendelin deneysel titizliğinin bir diğer unsuru da test çaprazlamasıdır. Test çaprazlaması, bir gametin hangi faktörleri taşıdığını belirlemek için çekinik ve saf soy bir bireyden üretilmiş gametle döllenmesidir. Çekinik bireydeki gamet sadece çekinik faktörü taşıyacağı için döllenme sonrasında oluşan bireyin gösterdiği özellik, tamamen bilinmeyen gamet tarafından belirlenecektir.

Mendel deneyleri, genetik analiz açısından bir kullanım kılavuzu niteliğindedir. Model organizmanın ve özelliklerin seçiminden çaprazlama tekniklerine kadar her ayrıntı ince hesaplanmıştır. Çaprazlamanın tarımda ve hayvancılıkta kullanımı, yeni soyların elde edilmesi, özellikle Mendel'in yetiştiği Orta Avrupa'da gelişmiş bir gelenekti. Ancak, çaprazlamayı analitik bir teknik olarak kullanmak, yani bir

organizmanın genetik yapısını belirlemek için bir araç haline getirmek Mendel genetiğinin özüdür.

Mendel'in 1866 makalesi 1900 yılına kadar gözden uzak kaldı çünkü pek tanınmayan bir dergide yayınlanmıştı. 1900 yılında üç bilim insanı - Carl Correns, Erich von Tschermak ve Hugo De Vries - bağımsız olarak aynı sonuçlara ulaştılar. Mendel'in çalışmaları yeniden keşfedildikten sonra özellikle ABD'de yeni bir araştırma programına dönüştüler. Columbia Üniversitesi'nde Thomas Hunt Morgan ve öğrencileri Mendelci genetik analizi yeni bir türe - sirke sineğine - taşıdılar.

Mendel genetiğinin teorik yapısının inşasında T. H. Morgan ve öğrencilerinin Kolombiya Üniversitesi'ndeki sinek odasında yaptıkları çalışmalar çok önemlidir. Ancak bundan önce, gen-genotip-fenotip kavramlarını tanımlayan Wilhelm Johannsen'in 1911 makalesinden bahsetmemiz gerekiyor. Çünkü bu makale, Mendel genetiğinin gelişkin bir versiyonu olan klasik aktarım genetiğinin kuramsal yapısı üzerinde çok etkilidir.

Kalıtımın genotip kavrayışı yerleşmeden önce, bireylerin "kişisel özelliklerinin" (gözlenebilir biyolojik özelliklerinin) kalıtıldığı sanılıyordu. Yani ebeveynler ile yavrular arasındaki benzerlik, ebeveynlerin biyolojik özelliklerinin (örn. çiçek rengi, vücut ağırlığı, vb.) aktarılmasına dayanıyordu. Ama Johannsen için aktarılan şey ile gelişim sonucunda ortaya çıkan özellikler tamamen farklı şeylerdir. Johannsen'e göre ebeveynin fenotipi yavrunun fenotipini belirlemez, her ikisi de genotip tarafından belirlenir.

Kişisel özelliklerin kalıtılmasıyla bağlantılı bir diğer düşünce de Weissmann'ın preformasyonist görüşleridir. Bu görüşe göre organizmalarda birim özellikler vardır ve bu özelliklerin gametlerde taşınan karşılıkları vardır. Preformasyonculuk ve bunun Mendelci versiyonu olan birim-özellik hipotezi, organizmayı bu birim özelliklerin toplamı olarak, kalıtsal materyali ise bu birim özelliklerin planını taşıyan bir yapı olarak görür. Ancak Johannsen açısından kalıtımın birimlerinden söz edilebilse bile

bunlar biyolojik özelliklerle birebir ilişki içinde değildir. Johannsen, kalıtımın bu kesikli birimlerine (yani Mendelci genetik analizin birim faktörlerine) genler adını verir. Genotip ise "bir gametteki veya zigottaki tüm genlerin toplamıdır".

Johannsen, genleri birer potansiyel olarak tanımlar. Bu potansiyellerin biyolojik özellikleri ortaya çıkarmaları, çevreye ve diğer genlerin potansiyellerine bağlıdır. Genotip, bu potansiyellerin bileşkesidir. Bu açıdan bakıldığında genotip bir reaksiyon normudur. Çevreyle etkileşim sonucunda ortaya çıkabilecek fenotip çeşitliliğinin sınırlarını belirleyen bir norm. Bu kavrayışta genler ve fenotip arasında hiçbir çizgisel ilişki varsayılmaz. Ama yine de genotip, çevre ve fenotip arasında katı bir nedensel ilişki vardır. Aynı genotip aynı çevresel koşullarda mutlaka aynı fenotipe yol açar. Genotip, fenotipin gelişiminin tarihsiz ve yapısal bir belirleyenidir. Genotipler kimyanın yapısal formüllerine benzerler.

Johannsen'e göre sürekli değişkenlik gösteren fenotipik özellikler (örn boy), süreksiz genetik değişkenler ve sürekli değişkenlik gösteren çevrenin ortak etkisiyle açıklanabilirler. Yani ilk bakışta Mendel genetiğinin varsayımlarıyla çelişir gibi görünen özellikler bile bu çerçevede incelenebilirler. Sürekli değişkenliğin önemi, Darwin'in doğal seçilim yoluyla evrimi sürekli-dereceli değişkenliğe dayandırmasında yatar. Fenotipte sürekli değişkenlikle genotipte kesikli değişkenliğin uzlaştırılması, Modern Sentez'in çözdüğü en önemli problemlerden biridir.Johannsen bu sorunu şöyle çözer: sürekli değişkenlik gösteren özellikler çok gen tarafından belirlenen özelliklerdir. Birçok gendeki süreksiz değişkenliğin toplam etkisi, sürekli değişim gösteren çevresel etkenler (örn. sıcaklık, azot miktarı, vb.) ile birlikte sürekli fenotipik değişkenliği açıklar.
Johannsen'in makalesi genetik açısından bir mihenk taşıdır çünkü kalıtımın kesikli, fenotipik değişkenliğin sürekli olabileceğini gösteren ilk makaledir. Morgan ve öğrencileri işte bu temel üzerinde çalışırlar. Karşılaştıkları anormal durumları bu kuramsal çerçevenin analitik gücüne güvenerek aşarlar.

T. H. Morgan ve öğrencileri, sirke sineğinde (Drosophila melanogaster) morfolojik özelliklerin (örn. kanat şekli, göz rengi) ve bunların mutasyonlarının genetik analizine dayanan bir araştırma programı kurdular. İlk önemli buluşları, beyaz gözlere yol açan bir mutasyonun X kromozomu üzerinde taşındığını göstermekti. Diğer ve daha önemli olan keşifleri ise genlerin bağımsız olarak ayrışmadığıydı. Genler, kromozom üzerinde birbirine ne kadar yakınsa, gamet oluşumunda birlikte hareket etmelerinin olasılığı o kadar yüksek oluyordu. Bu nicel ilişki aracılığıyla ilk kromozom haritasını 1912 yılında ortaya çıkardılar. Yani genlerin (daha doğrusu mutasyonların) bir kromozom üzerindeki konumlarını gösteren ilk basit haritayı oluşturdular.

Morgan ve diğer Mendelcilerin genetik analizde karşılaştıkları en önemli problem, açık ve seçik olarak Mendelci bir kalıtım yolu izlemeyen karmaşık özelliklerde ortaya çıkıyordu. Sirke sineğinde kanat şekliyle ilgili kimi mutasyonlar ve sıçanlarda tüy rengini etkileyen bir mutasyon buna örnek gösterilebilir. İki mutasyon da ne kadar çok kuşak boyunca seçilirse seçilsin, yüzde yüz frekansa ulaşılamıyordu. Bu mutasyonların seçildiği popülasyonlarda özellikler dereceli olarak dağılıyordu. Örneğin sıçanlarda başlıklı (hooded) özelliği, sadece kafa ve boyun bölgesinde siyah tüylere sahip sıçanlardan vücudunun neredeyse tamamı siyah tüylerle kaplı sıçanlara kadar uzanan bir spektrumda değişkenlik gösteriyordu. Ama mutasyonun kalıtsal olduğu da kesindi çünkü bu özellikleri az derecede gösteren bireylerin yavruları bile rastgele bir bireye göre çok daha yüksek frekansla aynı özelliği gösteriyorlardı.

Başlıklı sıçanlar üzerine çalışmaları yürüten Castle ve Phillips, bu sonuçları seçilimin genleri değiştirdiğinin bir kanıtı olarak yorumlamışlardı. Ama ortodoks bir Mendelci, başlangıçtaki popülasyonun saf olmadığını, yani birçok gen açısından polimorfik olduğunu söylerdi. Morgan'ın öğrencilerinden Hermann J. Muller tam olarak bunu yaptı. Başlangıç popülâsyonunun birçok gen açısından heterojen olduğunu, bu genlerden birinin özelliğin varlığını/yokluğunu belirlediğini, diğerlerinin ise modifiye edici olduğunu iddia etti. Ancak 1914'te Muller sadece bu türde sorunlu

fenomenlerin katı Mendelci bir çerçevede açıklanabileceğini göstermişti. Yani bu tür fenomenlerin açıklanmasının teorik olarak olası olduğunu göstermişti. 1920'de ise Edgar Altenburg ve Muller, Mendelci genetik analizin bu tipte sorunlara somut olarak nasıl uygulanabileceğini gösterdiler.

Bu çalışmayı derinlemesine anlatamayız. Ancak bazı önemli noktalara değinebiliriz. Öncelikle bu çalışmada sirke sineğinin kanatlarının uçlarına kesik (truncate) biçim veren bir mutasyon kümesi inceleniyor. Başlıklı sıçanlarda olduğu gibi bu özellik de ne kadar seçilirse seçilsin saf bir popülasyon elde edilemiyordu. Özellik kalıtsaldı ama birden çok faktörün etkisi altındaydı. Bu çalışmanın ayırt edici yanı, bu karmaşık kalıtım örüntüsüne neden olan genetik altyapının çözümlenebilmiş olması. Yani karakter üzerinde etkili olan genlerin kromozomlardaki yerlerinin saptanması ve karakter üzerindeki etkilerinin birbirinden ayrıştırılabilmesi kısmen de olsa başarılabilmişti. Bu çalışmada baş faktör (gen) ve modifiye edici faktörlerin (genlerin) yerleri saptanabilmişti (toplam üç gen). Hatta bu genlerin aktarımı o kadar kolayca takip edilebilir hale gelmişti ki, istenen genleri taşıyan kromozomları çaprazlama yoluyla birleştirip istenen özelliklerde bireyler ortaya çıkarmak bile mümkün olmuştu.

Bu iki örnek, Mendelci genetiğin genler ile biyolojik özellikler arasında kurduğu ilişki hakkında temel çerçeveyi açık etmemize olanak veriyor. Bu çerçevede takip edilebilirlik merkezi öneme sahip. Mendel, görsel olarak en kolay takip edilebilen ikili karakterlerin aktarımını, matematiksel olarak da takip edilebilir hale getirmişti. Mendelciliğin geliştiricileri ise, daha karmaşık özellikleri bile takip etmeyi sağlayacak yöntemler geliştirdiler. Ama yöntemleri gen denilen soyut varlığı doğrudan incelemeye olanak vermiyordu. Daha ziyade kolayca gözlenebilen etkilere sahip mutant formların genetik karşılıklarıyla ilgileniyorlardı. Gelişim konusunda çoğunlukla sessiz kalıyorlardı. Bu konuda konuştuklarında ise tıpkı Johannsen gibi, genler ile fenotipik özellikler arasındaki ilişkinin birebir değil çoka çok biçiminde olduğunu söylüyorlardı. Ancak yine de, karmaşık mutasyonların analizinde

gördüğümüz üzere, karmaşık fenotipi, baş genler ve birkaç modifiye edici gendeki çeşitlilikle açıklıyorlardı. Kısaca ifade etmek gerekirse, Mendel genetiğinde genler ile fenotipik özellikler arasındaki ilişki çizgisel ve aza-az bir nedensel ilişkiydi. Böylece çok karmaşık bir ilişkiyi takip edilebilir hale getirmeyi başarmışlardı.

Bu çalışmalardan çıkan bir diğer önemli sonuç da genlerin kalıcılığı fikrinin güç kazanmasıydı. Mendelciliğin temelleri, yani genlerin bağımsız birer varlık oldukları, birbirine karışmadıkları, ayrıca kuşaklar boyunca değişmeden aktarıldıkları tezleri gen merkezciliğin temelinde duran düşünceledir. Genlerin doğası, yani ne tür fiziksel özellikleri olduğu, yapı taşlarının ne olduğu, Mendel genetiğinin geliştiricilerinin çoğunlukla es geçtiği bir konudur. Burada belki de tek istisna Hermann J. Muller'dir.

Hermann J. Muller tıpkı diğer Mendelciler gibi, genlerin seçilimde veya aktarımda dönüştüğü fikrini reddetmişti. Karmaşık aktarım örüntüsü gösteren özelliklerin çok genle kalıtıldıklarına ve bu özellikler açısından görülen sürekli-dereceli çeşitliliğin, çalışılan popülasyonların bu genler açısından heterojen olmasıyla açıklanacağına inanıyordu. O da Johannsen gibi genler ile özellikler arasında çoka çok ilişkiler olduğunu, hatta genlerin biyolojik özellikleri bir çizgisel patika ile değil, bir ağ biçiminde, kendi aralarında da etkileşerek (epistasis) belirlediklerini düşünüyordu. Ancak aynı çağda yaşadığı genetikçilerden farklı olarak, genleri sadece işe yarar birer soyutlama olarak değil, gerçek birer varlık olarak görüyordu. Muller bu konudaki spekülasyonlarını mutasyonların genetik analiziyle, biyokimyayla ve kromozom mekaniğinin mevcut bulgularıyla temellendiriyordu. Ama genler hakkındaki en önemli iddiası, doğal seçilim ve genetik arasındaki ilişki hakkındaki derin kavrayışında yatıyordu.

Muller genlerin doğası hakkındaki ilk bilimsel makalesini 1922'de yayınladı. Bu makalede genlerin ultramikroskopik parçacıklar olduğunu ve genlerin organizmayı "tüm hücresel içeriklerin doğasını belirleyerek" şekillendirdiğini iddia etti. Muller, genler ile onların etkileri arasında bir ayrım yaptı. Hücrenin yaşamsal işlevleri

enzimlerde yatıyor olabilir, ama bu genlerin enzimler olmak zorunda olduğu anlamına gelmez. Zaten Muller açısından genlerin özsel özelliği, hücre içeriklerini belirlemek değil, kopyalanabilmektir. Kopyalamada hammadde sitoplazmadan gelebilir. Genin yaptığı şey, kendi kopyalanmasıyla sonuçlanan kimyasal tepkimeyi yönetmektir.

Muller'e göre genler, kendilerini kopyalamanın yanında, kendilerinde mutasyon aracılığıyla gerçekleşen değişiklikleri de kopyalayabilirler. Diğer bir deyişle, mutasyonlar genin ve sonuçta ortaya çıkan fenotipin yapısını değiştirse bile, bu, genlerin kendilerini kopyalama yeteneklerini ortadan kaldırmaz. Muller bu özelliğe, mutasyona uğrayabilen otokataliz adını verir: hem kendi kopyalanmasını, hem de değişimlerinin kopyalanmasını anlatmak için.

Değişimlerini de kopyalayabilme yeteneği Muller için önemliydi çünkü bu genlerin doğal seçilim yoluyla evrilebilirliğinin anahtarıydı. Muller'in bu makalesini sunduğu toplantıda ünlü genetikçi Bateson, evrimin özünün kalıtım ve çeşitlilik olduğunu söylemişti. Muller ise evrimin özünün çeşitliliğin kalıtımı olduğunu söyler. Çeşitliliğin (mutasyonların) kalıtılması, evrimi ve "birikimi, rekabeti ve kendini çoğaltan çeşitliliğin seçici biçimde yayılmasını" garanti altına alır. Böylece canlı ve cansız dünya arasındaki ayrımı açıklar. Bu maddi örgütleniş ile inorganik dünya arasındaki geniş boşluğun nedeni, seçilime tabi olan değişebilir ve değişimlerini kopyalayabilen maddenin karmaşıklık, çeşitlilik ve uyarlanma ortaya çıkarma kapasitesindeki farkta gizlidir.

Muller'in 1927'de *Science* dergisinde yayınlanan makalesi, yapay mutasyonlar ve bunların genetik analizi aracılığıyla genlerin doğası hakkında kimi bulgulara ulaşılabileceğini gösteriyordu. X ışını radyasyonu, mutasyon hızını 145 katına çıkarmıştı. Daha fazla mutasyon, daha derinlemesine genetik analiz anlamına gelir çünkü ne kadar çeşit genotip varsa, çaprazlamadan elde edilecek yeni genotip çeşidi de o kadar fazladır. Eğer bu genotipik farklar, fenotip farklarına yansıyorsa, bağlantı

analizi sayesinde daha detaylı - daha çok kromozom pozisyonunu içeren - haritalar üretilebilir.

Muller'e göre mutasyon hızını yükselten bu girişimsel teknikler, genlerin doğasını aydınlatma açısından kısmen işlevsel olabilir. Muller, 1927 tarihli çalışmasında, genlerin bileşik bir içsel yapıya sahip olduklarını, yani bölünemez birer atom olmadıklarını ortaya çıkarmıştı. Ancak genin iç yapısında ortaya çıkan değişimler, klasik Mendelci birimler gibi aktarılmaya devam ediyordu. Yani bileşik içsel yapı, rekombinasyonda yeniden karılma ile sonuçlanmıyordu.

Genetik analizin gen yapısı ile ilgili söyleyebilecekleri sınırlıdır. Bunun nedenlerinden biri, genin farklı kısımlarında meydana gelen mutasyonların aynı fenotipik sonucu doğurmasıdır. Böyle bir durumda klasik aktarım genetiği genotip farklarına karşı kör olacaktır çünkü klasik genetikte genotip farkı, fenotip farkından çıkarsanır - doğrudan gözlenemez. Bir başka neden ise X-ışını ve diğer mutajenik faktörlerin etkilerinin özgül olmamasıdır. X-ışını ile mutasyon yaratmak genlere nokta atışı yapmaya benzemez. Daha ziyade saçmalı tüfekle ateş etmeye benzer. Aynı anda birden çok kromozom bölgesi etkilenir. Bu yüzden tekil genlerin içsel yapılarını aydımlatmak için daha doğrudan ve daha özgül araçlar gerekirdi. Bu ise ancak moleküler biyoloji ile mümkün olmuştur.

Muller genler hakkındaki görüşlerine son şeklini - 1927 itibariyle - verdiğinde genetik materyalin DNA olduğu keşfedilmemişti. Genetiğin molekülerleşmesi, yani moleküler biyolojinin araştırma yöntemleriyle incelenmesi gen kavramını da dönüştürdü. Mendelci genden moleküler gene geçişte enformasyon kavramı çok önemlidir.

Mendel genetiğinde genler, yerleri bağlantı analiziyle saptanan, kromozomlar üzerine tespih taneleri gibi yerleştirilmiş soyut varlıklardır. Etkileri aracılığıyla bilinirler. Daha doğrusu, çeşitli formlarının etkileri ve bu formların işaretleyici genler (marker) ile bağlantı kuvvetlerine dayanarak incelenirler.

Mendelci gen istatistiksel bir soyutlamadır. Bir kromozom bölgesinin (lokus) üç farklı form tarafından işgal edilebileceğini düşünelim. Bu formlara alel, veya eski Mendel genetiğindeki adıyla alelomorf denir. Bu formların ise üç farklı fenotiple korelasyon gösterdiğini düşünelim: sarı, kırmızı ve beyaz çiçek rengi. Aleller kendi başlarına alternatif formları (çiçek renklerini) belirlemezler. Ama farklı alellere sahip canlılarda, diğer tüm koşullar (örn. diğer lokuslar, çevresel koşullar) sabit kalmak koşuluyla, fenotipik farkların nedeni alel farklarıdır. Yani Mendelci gen fenotipik özelliği değil, fenotipik özelliklerdeki farklılığı açıklar. Mendelci yaklaşım, bir çiçeğin neden kırmızı olduğunu açıklamaz. Bir kırmızı çiçekle bir beyaz çiçek arasındaki farkı, yani birinin kırmızı olmasını ama diğerinin beyaz olmasını, diğer tüm koşullar sabit kalmak kaydıyla, tek gendeki farklılıkla açıklar. Bu yaklaşımda genlere kısaca "beyaz geni", "kırmızı geni" denebilir. Ama bu, adı üzerinde, sadece bir kısaltmadır.

Moleküler gen ise proteinlerin amino asit dizisini belirleme kapasitesiyle tanımlanır. Dizi belirleme, yani kodlama, enformasyonel bir kavramdır. Enformasyon kavramının biyolojide ve özellikle genetikte kilit kavramlardan biri haline gelmesi, moleküler biyolojinin ortaya çıktığı 1940-1960 aralığında yaşanan deneysel ve kavramsal atılımın bir parçasıdır.

Moleküler biyolojinin doğum sürecinde enformasyon kavramından önce gelen, hatta enformasyon kavramının içeriğini belirleyecek derecede önemli olan kavram "özgüllük"tür. Özgüllük kavramı moleküler düzeyde işlev-yapı koşutluğunu sağlayan temel kavramdır. Biyokimyasal özgüllük, her enzimin kendine has bir reaksiyon türünü sentezlemesi olarak anlaşılabilir. 1940larda biyokimyasal genetik çalışmalarında özgüllük, enzimlerin veya antikorların sübstratlar ve antijenlerle girdikleri özgül kimyasal ilişkileri anlatıyordu. Bir gen bir enzim hipotezine göre genler, enzimlerin, yani bir protein türünün özgüllüğünü belirlemesiyle tanımlanır. Biyokimyasal özgüllüğün fiziksel temelinin proteinin üç boyutlu yapısı olduğu görüşü 1940'larda Linus Pauling tarafından ortaya atılmıştır. Pauling'e göre antikorların antijenlerini tanımaları, enzimlerin sadece belirli reaksiyonları

katalizlemeleri, yani *özgül işlevlerini* yerine getirebilmeleri, bu protein makineleri ile üzerinde işledikleri maddeler arasında 3 boyutlu şekil açısından bir uyum olmasından kaynaklanıyordu. Genlerin proteinlerin 3 boyutlu yapılarını nasıl belirledikleri ise 1950lerde ortaya atılan dizi hipotezi ile anlaşılabilir.

Dizi hipotezine göre bir genin özgül yapısı onun nükleotid dizisidir ve bu dizi, amino asitlerin dizlişini belirleyen bir koddur. Amino asit dizisinin, yani proteinin birincil yapısının belirlenmesi ile üç boyutlu yapının da otomatik olarak belirlendiği varsayılır. Başka bir deyişle, protein katlanma problemi fizik ve kimyanın yasalarına havale edilir.

Dizi hipotezi, takipçisi olan merkezi dogma ile birlikte, genetik enformasyon kavramının ilk kez açık ve seçik bir tanımının verilmesine olanak sağlamıştı. Moleküler biyolojinin merkezi dogması, enformasyon iletiminin nükleik asitlerden (DNA ve RNA) proteinlere doğru olduğunu, ama proteinlerden nükleik asitlere doğru enformasyon transferi olamayacağını söyler. Burada enformasyon iletimi, nükleik asitlerin özgül nükleotid dizilerinin, proteinlerin özgül amimo asit dizilerini belirlemesidir. Öyleyse merkezi dogmaya göre enformasyon, genetik materyalin düzenidir. Enformasyon iletimi ise genetik materyalin düzeninin moleküler bir fenotipin (protein yapısı) düzenine *çevrilmesidir*.

İki düzen arasındaki çeviri kurallarının ne olduğunu belirleme problemine "genetik kod" problemi denir. Bir başka ifadeyle, genetik kod problemi, özgül nükleotid dizilerinin hangi özgül amino asit dizilerine denk düştüğünü belirleme problemidir. Bu problem, hem kuramsal hem de deneysel girdiler sayesinde çözülebilmiştir.

Genetik kod probleminin çözümüne giden yolda önemli kuramsal girdilerden biri, nükleotidlerin dört çeşit, amino asitlerin 20 çeşit olmasından yola çıkılarak oluşturlan "3 nükleik asit = bir amino asit" denkliğidir. 4 çeşit nükleik asidin ikili bir dizisi sadece 16 amino asidi belirlemeye olanak verirdi. Dörtlü bir kombinasyon ise 256 farklı dizi üretebilir, bu da gerekenden fazla olurdu. Üçlü dizi, 64 farklı

kombinasyona denk düşer. Bu sayı da 20'den fazladır. Genetik kod probleminin çözümünde kuramsal çabaların odak noktasını 64 olasılığı 20'ye düşürmek yer alır.

Aslında eğer kod dejenereyse, yani birden fazla nükleik asit üçlüsü tek amino asiti belirliyorsa, problem ancak ve ancak protein sentezinin biyokimyası ile çözülebilir. George Gamov ve Francis Crick ise bu olasılığı kuramsal bir nedenle reddetmişlerdir: dejenere bir kod, enformasyon kaybına neden olur. Genetik kodun çözümü için ortaya atılan kuramsal şemaların temel sorunu, canlılarda protein sentezini kusursuz bir enformasyon aktarımı olarak görme hatasıdır.

Genetik kod probleminin çözümünde protein sentezinin biyokimyası ile ilgili deneysel çalışmalar kuramsal spekülasyonlardan daha etkili oldu. Hücre dışı protein sentezi düzeneklerinin kurulması ile protein sentezinde girdiyi ve çıktıyı kontrol altına almak olası hale geldi. Yapay nükleik asitlerin üretilmesi ve bunların sisteme girdi olarak eklenmeleri, genetik kod probleminin çözülmesinde bir mihenk taşıydı. İlk yapay RNA, sadece urasilden oluşuyordu ve çıktı olan protein sadece fenilalanin amino asidinden oluşuyordu. Öyleyse UUU nükleotid üçlüsü, fenilalanini kodluyordu. Benzer yöntemlerin kullanılmasıyla genetik kod 1960lı yıllarda çözüldü. Kod dejenereydi, yani enformasyon transferi tam verimlilikle çalışmıyordu. Kodun çözülme biçiminin gündeme getirdiği önemli sonuçlardan biri de enformasyon iletimiyle ilgili kuramsal koşulları tatmin etmeye dayanan araştırma yolunun iflas etmesiydi. Kod problemi, matematiksel değil biyokimyasal yöntemlerle çözülmüştü.

Gerek dizi hipotezi ve merkezi dogmanın, gerekse kod probleminin sınırları içinde bakıldığında genetik materyal, statik bir enformasyon kaynağıdır. Bir canlı ise yaşamı boyunca çeşitli çevresel etmenlere adaptif tepkiler vermek zorundadır. Adaptif tepki, zamana ve koşullara duyarlı, yani dinamik bir sistem gerektirir. Statik bir enformasyon kaynağı olarak genetik materyalin proteinlerin yapısını belirlediği, proteinlerin girdiği etkileşimlerin ise canlının çevresiyle kurduğu dinamik etkileşimi açıklamakta yeterli olduğu düşünülebilir. Ama bu etkileşimin genlerin aktivitesini ilgilendiren bir boyutu da vardır. Hangi proteinin nerede ve ne zaman

sentezleneceğinin belirlenmesi genetik enformasyon kavramının ikinci boyutunu oluşturur.

Bakterilerde ikili büyüme eğrisi problemi, protein sentezinin nasıl kontrol edildiğini anlamanın ilk adımı olmuştu. İkili büyüme eğrisi problemini kısaca şöyle ifade edebiliriz. Bir *E. coli* kolonisinin yaşadığı ortamda glukoz ve laktoz bulunduğunda bakteri kolonisi önce üstel bir büyüme eğrisi gösterir, sonra büyüme duraklar. Bir süre sonra koloni tekrar üstel bir eğriyle büyümeye devam eder ve besin tamamen tükendiğinde büyüme durur. *E. coli* hem glukozu hem de laktozu metabolize edebilir. Öyleyse,iki büyüme dönemi arasındaki duraklamanın nedeni nedir? 1959 yılında tamamlanan PaJaMo (Pardee-Jacob-Monod) deneyinden çıkan sonuca göre bakteriler önce glukozu metabolize ederler, sonra laktozu metabolize edecek enzimi - Beta galaktosidaz - sentezlemeye başlarlar. Beta galaktosidazın sentezlenmesi zaman aldığı için geçici bir duraklama yaşanır.

PaJaMo deneyinden önce enzimin bakteride zaten var olduğu, ama aktive edilmesi için zaman gerektiği düşünülüyordu. Bu deneyden türetilen operon modeline göre laktozun varlığı enzimi aktive etmez, enzimin sıfırdan sentezlenmesine yol açar. Operon, düzenleyici bölgeler ve yapısal genlerden oluşan bir sistemdir. Düzenleyici bölgelere bağlanan baskılayıcı protein bu bölgenin yakınındaki genlerden protein sentezlenmesini engeller. Bu protein laktozun varlığında DNA'dan ayrılır ve protein sentezi gerçekleşir.

Bakterilerde gen ifadesini düzenleyen mekanizmanın keşfinde düzenleyici proteinlerin yapısı ile ilgili de önemli bilgilere ulaşılmıştı. 1940'larda enzimlerin ve diğer özgül işlevli proteinlerin 3 boyutlu yapıları sayesinde bu işlevleri yerine getirebildikleri iddiası ortaya atılmıştı. Düzenleyici proteinlerin ise iki açıdan özgül olmaları gerekir: hem aktivitelerini düzenleyen moleküller açısından hem de aktivitesini düzenledikleri molekül açısından. Daha somut konuşmak gerekirse, düzenleyici molekülün bir bölgesi ligand adı verilen molekülle özgül bir etkileşime girerken diğer bir bölgesi DNA'nın özel bir bölgesiyle özgül bir etkileşime girer. Ligandın bağlanması bu proteinin DNA'ya bağlanan kısmında bir konformasyon

değişimini tetikleri. Bu tür proteinlere “allosterik” yani alternatif konformasyonlara sahip proteinler denir.

Operon modeli ve allosteriden çıkan kuramsal sonuçlardan belki de en önemlisi, genetik materyalin yalnızca protein yapısını belirleme anlamında değil, protein sentezinin hangi koşullarda aktive edilip hangi koşullarda engelleneceğini belirleme anlamında da enformasyon taşımasıdır. Bu ikinci ve daha zengin genetik enformasyon kavramına “genetik program” adı verilir. İlk kez 1961’de yazılı kaynaklarda yer bulan genetik program kavramının, bakterilerde protein sentezinin düzenlenmesini çok aşan, geniş geniş bir kapsamı vardır. Örneğin çok hücreli canlılarda gelişim, hücre farlılaşmasını gerektirir. Her beden hücresi aynı genetik materyali taşıdığına göre farklılaşma, protein sentezindeki farklara dayanmalıdır. Yani bazı dokularda bazı genler aktive olurken diğerlerinde başka genler aktive olmalıdır. Gelişimin dinamiğini - zamansal ve mekansal bağlama duyarlı oluşunu - genetik program düşüncesiyle açıklamak mümkündür.

Genetik program düşüncesinin çağrışımlarına bu yazının sonunda tekrar döneceğiz. Şimdilik bir hatırlatma daha yapmamız gerekiyor. 1961’de Jacob ve Monod dışında genetik program fikrini ifade ettikleri tarihte Ernst Mayr da aynı kavramı evrimsel bağlamda canlıların ayırt edici niteliğini tanımlamak için kullanmıştı. Evrim kuramıyla genetiğin bir araya gelişi, bu kavramsal yakınlaşmanın imlediğinden daha çetrefilli bir yol izledi.

Evrim ile genetiğin yakınlaştığı süreci anlamak için Mendel genetiğine geri dönmek zorundayız. Mendel genetiğinde temel çeşitlilik tipi kesiklidir. Birbirinden kolayca ayırt edilebilecek morfolojik farklar Mendelci genetik analizin hammaddesini oluşturur. Mendel’in çalışmalarındaki özellikler, ikililer şeklindeydi: sarı/yeşil, düz/buruşuk, uzun/cüce, vb. Bu uç değerlerin arası boştu.

Darwin ise evrimin temel mekanizması saydığı doğal seçilimin tedrici yönünü vurgulamıştı. Darwin’e göre doğal seçilimin üzerinde işlediği çeşitlilik biçimi sürekliydi, yani Mendel genetiğindeki gibi sıçramalı değildi. Bu fark ilk bakışta evrim

kuramı ile Mendel genetiği arasında uzlaşmaz bir çelişki olduğu yönünde yorumlanmıştı.

Uzlaşmaz çelişki görüntüsünü yaratan bir varsayım da mutasyonun doğal seçilime alternatif bir evrim mekanizması olarak görülmesiydi. Gerçekten de mutasyon kuramı, Hugo De Vries'in ilk formüle ettiği biçimiyle, Darwinci tedrici evrime alternatif olarak ortaya atılmıştı. De Vries, Darwin'in kuramında temel bir eksiklik olduğunu söylüyordu. De Vries'e göre evrim kuramı gözleme ve spekülasyona dayanıyordu ama deneysel yönü eksikti. Evrimi deneysel olarak çalışılabilir bir alan haline getirmek türleşme gibi olayların bir bilim insanının gözleyebileceği zaman aralığında gerçekleşmesi gerekiyordu. De Vries *Oenothera Lamarckiana* bitkisinde yeni türlerin oluşumunu gözleyebildiğini söylemişti. Mutasyon kuramına göre organizmalar mutasyon dönemine girdikleri zaman yeni türler tek kuşakta ortaya çıkabiliyordu. Mutasyon kuramındaki anlamıyla mutasyon, bir organizmanın çok çeşitli özelliklerinde, aynı anda ortaya çıkan kalıtımsal değişimlere verilen addır. Örneğin De Vries, *O. Lamarkciana*'da yaprak boyu ve şekli, çiçek türü, gövde uzunluğu açısından atasal türden radikal biçimde farklılaşmış bireyler gözlemlemişti.

Thomas H. Morgan, sirke sineğinde genetik çalışmalara başlarken De Vries türü mutasyonları bu türde de gözleme umudundaydı. Ancak sirke sineği genetiği çalışmalarında incelediği mutasyon sayısı arttıkça, Mendelci mutasyon ile De Vries'in "tür yaratan" mutasyonları arasındaki fark iyice belirginleşmişti. 1909'dan önce sıkı bir Darwin karşıtı olan Morgan, 1909-1916 aralığında daha uzlaşmacı bir pozisyona yerleşti. Morgan ve öğrencilerinin gözledikleri mutasyonlar ne kadar büyük değişimlere neden olsalar da yeni türler yaratacak türden değişimler değillerdi.

Mendel genetiğinde kavramsal ilerlemelerden biri olan çok faktörlü kalıtım düşüncesi, sürekli varyasyon/kesikli varyasyon ikiliğinin aşılması açısından da önemliydi. Sürekli varyasyon gösteren fenotipik özelliklerin genetik temelinde, her birinin etkisi küçük bir çok genetik varyantın olabileceği fikri Muller tarafından 1914'te ortaya atılmıştı. Ancak bu fikrin kuramsal olarak genelleştirilmesi, Fisher'ın 1918'de yayınlanan makalesiyle mümkün oldu.

Sürekli varyasyon/kesikli varyasyon tartışması, biyometriciler ile Mendelciler arasındaki temel ayrımdı. Modern evrim kuramının ortaya çıkışında - modern sentezin doğuşunda - biyometrinin genellemeleri ile Mendel genetiğinin aktarım mekanizmasının uzlaştırılması önemli bir uğraktır.

Biyometri, ölçülebilir, sürekli varyasyon gösteren kalıtımsal özelliklerin niceliksel olarak incelendiği bir alandır. Francis Galton tarafından 19. Yüzyılın sonlarında geliştirilen istatistiksel teknikler, deneysel incelemenin olası olmadığı insan fenotipik özelliklerini (boy, zeka vb.), hayvan yetiştiricilerinin ıslah çalışmalarının konusu olan karakterleri (süt verimi vb) incelemeye olanak sağlamıştı. Ebeveyn/yavru korelasyonu biyometrinin kalıtım kuramına en önemli katkısıydı.

Biyometriciler Mendel genetiğinin evrim kuramıyla uyumsuz olduğunu, çünkü sürekli varyasyonu açıklayamayacağını düşünüyorlardı. Yirminci yüzyılın başlarında Udny Yule, çok sayıda Mendelci genin etkilediği ve baskınlığın kısmi olduğu fenotipik özelliklerin sürekli varyasyon göstermesinin mümkün olduğunu göstermişti. Ancak biyometriciler bu türde çalışmalara şüpheyle bakıyorlardı çünkü onlara göre çok fazla genin bir özelliği belirlediğini söylemek Mendel genetiğinin ruhuna aykırıydı ve tam baskınlık Mendel genetiğinin vazgeçilmez bir ilkesiydi.

Ronald Fisher'ın 1918'de yayınlanan makalesinde her birinin etkisi sonsuz küçük, sınırsız Mendelci faktörün belirlediği bir özelliğin sürekli varyasyon göstermesi kanıtlanır. Fisher, tam baskınlık varsayımını da rafa kaldırır. Biyometriciler Fisher'a tıpkı Yule'a itiraz ettikleri gibi itiraz ederler. Çok fazla genin tek karakteri etkilemesi ve baskınlığın dereceli olması görüşlerinin Mendelci araştırmayla uyuşmadığını iddia ederler.

Fisher'ın bu makalesiyle Modern Sentez adı verilen, güncellenmiş evrim kuramının ortaya çıkışını hazırladığı söylenebilir. Modern Sentez, yirminci yüzyılın ilk yarısında evrim kuramının genetik, paleoloji ve sistematiği birleştiren bir araştırma programına dönüşmüş halidir. Bu çalışmada genetik konu edildiği için sadece genetik ve evrim arasındaki ilişkilerden bahsedilmektedir.

Modern sentezin ilk aşaması, popülasyon genetiğinin ilk matematiksel modellerinin ortaya çıktığı dönemdir. Bu modeller, evrim sürecini, Mendelci bir popülasyonda çeşitli alel frekanslarındaki değişimler olarak sunarlar. Mendelci popülasyon kavramı genetiğe yeni bir boyut katmıştır. Klasik aktarım genetiğinde önemli olan ebeveynlerin ve yavruların genetik yapılarıdır. Çaprazlama deneyleri üç veya dört kuşak sürer. Popülasyon genetiğinde popülasyon, belli genetik yapılara sahip bireylerin sayıları ve oranları ile ifade edilir. Bu oranlardaki değişim, doğal seçilim, genetik sürüklenme, mutasyon, göç vb. kuvvetlerin etkisiyle açıklanır.

Popülasyon genetiğinin evrim sürecini alel veya kısmi genotiplerin oranlarındaki değişimler olarak sunması, "fasülye torbası genetiği" tartışmasının özüydü. Ernst Mayr 1959'da, *Türlerin Kökeni*'nin yayınlanışının 100. Yılı için düzenlenen bir sempozyumda, popülasyon genetiğinin evrimi fasülye torbasından bazı renklerde fasülyeleri atıp başka renklerde fasülyeleri eklemek gibi basit ve indirgemeci biçimde sunmasını eleştirmişti. Mayr'a göre popülasyon genetik modellerde temel hata, genlerin birer atom gibi görülmeleri, onlara değişmez ve diğer genlerden bağımsız uyum gücü değerleri atfedilmesiydi. Genler arası etkileşim hiçe sayılıyor, organizmanın bir bütün olarak çevreyle etkileştiği unutuluyordu.

Mayr'ın eleştirisinin Fisher, Haldane veya Wright'ın özgül modelleri konusunda haklı olup olmaması bir yana, önemli bir probleme parmak bastığı aşikardı. Popülasyon genetiğinin modellerinde evrimi matematiksel olarak takip edilebilir hale getirmek için bir çok sadeleştirici varsayım vardı. Sabit uyum gücü, etkileşimin hata terimi olarak görülmesi, tek lokusta iki alelli modellerin tercih edilmesi bu sadeleştirmelerden bazılarıydı. Elbette daha karmaşık modeller kurmak ilkece mümkündü, ama ilk önce en basit modelin veriyi açıklayıp açıklamadığına bakılmalı, ancak açıklamıyorsa başka faktörler de modele dahil edilmeliydi.

Bu sadeleştirmelerin metodolojik değil de ontolojik bir bakış açısıyla yorumlanması, gen seçilimciliği olarak adlandırabileceğimiz evrim anlayışının temelini oluşturur. Gen seçilimciliği, modern ifadesini Richard Dawkins'in "bencil gen" metaforunda bulsa da, geçmişi daha eskiye dayanan bir görüştür. Bu görüşe göre genler, doğal

seçilimin temel birimleridir. Standart evrim modellerinde genler değil bireyler seçilime tabidir ama evrimin sonuçları gen frekanslarındaki değişim ile ifade edilir. Yani gen seçilimi, evrimsel değişimin nedeni değil sonucudur.

Genlerin seçilimin temel birimleri olduğu teziyle, doğal seçilimin kalıtımsal uyum gücü farklarına dayanmasını birbiriyle karıştırmamak gerekir. Kalıtımsal uyum gücü farkları, tikel genler arasındaki değil organizmalar arasındaki farklardır. Ancak popülasyon genetiğinde organizmalar kısmi genotipler olarak sunuldukları için ve genotipler arasındaki alel farklarından ortalama uyum gücü farkları hesaplanabileceği için, sanki seçilim genler üzerinde işliyormuş gibi bir görüntü ortaya çıkar. Başka bir ifadeyle, tüm evrim sürecinin Mendelci alellerin (bir genin alternatif formları) değiş tokuşundan ibaret olduğu, bu değiş tokuşta etkili olan evrimsel kuvvetlerin nesnesinin de öznesinin de genler olduğu gibi fazlasıyla indirgemeci bir ilüzyonla başbaşa kalırız.

Gen seçilimciliği, doğal seçilimin birimleri problemiyle sınırlı olmayan, daha geniş bir vizyonun parçasıdır. Bu vizyona kısaca gen merkezcilik adı verilir. Gen merkezcilik, yaşamın anahtarının genler olduğu fikridir. Daha somut konuşmak gerekirse, evrimi, gelişimi, metabolizmayı, davranışı ve canlılıkla ilgili tüm fiziksel etkinlikleri anlamak için genlerin özel bir konumu olduğunu kabul etmektir. Bu özel konumun bir boyutu, genlerin tüm yaşamsal süreçleri şöyle ya da böyle kontrol etmesidir. Ancak bu kontrol, doğrusal olmak zorunda değildir. Her biyolojik özelliğe denk düşen bir gen olduğu fikri gen merkezcilik için zorunlu değildir. Genlerin etkileri dolaylı olabilir. Gen merkezciliğe göre, hangi karmaşık patikayı izlerse izlesin, çevreyle nasıl etkileşirse etkileşsin, genler yaşamsal süreçlerin yöneticileridir. Genetik belirlenimcilik, yani bu yöneticilik fikri olmaksızın gen merkezcilik bir açıklama stratejisi olarak anlamsız olurdu.

Gen merkezcilik için genleri, gelişimi ve metabolizmayı etkileyen diğer etmenlerden ayıran özellik, bunların komut taşımalarıdır. Komut yoluyla belirleme, nedenselliğin özel bir biçimidir. Komutla belirlemede neden ve etki arasında sembolik, amaçlı ve organize bir bağlantı kurulur. İşte bu yüzden genler için program benzetmesi

kullanılır. Çevresel değişkenler ise hali hazırda genlerde bulunan komutların engellenmesi veya tetiklenmesi gibi basit ve amaçsız etkilerde bulunurlar.

Gen merkezcilik için bir çeşit genetik belirlenimcilik elzemdir, çünkü genlerin biyolojik açıklamalarda merkezi bir konumu hak etmeleri, nedensel açıdan kudretli olmalarına bağlıdır. Eğer kimi genotipler kimi fenotiplerle rastlantısal bir korelasyon gösteriyorsa veya genotip ve fenotip ortak bir nedene sahip oldukları için korelasyon gösteriyorsa, genler özel öneme haiz birer neden olmaktan çıkarlar. Genler, fenotiplerin ortaya çıkışında açık ve seçik birer nedensel faktör oldukları sürece önemlidirler. Genetik belirlenimcilik tartışması ise, özellikle insan davranışını belirleyen genetik nedenler aramak ile ilgili bir tartışmadır.

Genetik belirlenimciliğin ilkel versiyonları, genler ile davranış arasında doğrusal bir bağlantı kurma arayışı ile karakterize edilirler. Örneğin Charles Davenport, 1915 yılında yayınlanan bir makalesinde göçebeliğin cinsiyet kromozomlarına bağımlı bir Mendelci kalıtım yolu izlediğini savlar. Sirke sineğinde beyaz mutasyonu ile ABD toplumunda göçebe hayat tarzı eşitlenir. Davenport'un verisi eksik ve güvenilmezdir, göçebe hayatına mecbur kalan evsizlerin ve tarım işçilerinin toplumsal konumlarını es geçmiştir. Davenport bir genetik ıslah taraftarıdır. Toplumsal problemleri genetik ıslah ile çözmeye çalışmak 20. Yüzyılda ABD'de zorunlu kısırlaştırmaya, Hitler Almanya'sında ise zorunlu ötenaziye kadar uzanan vahşice yöntemlere yol açan bir perspektiftir.

Genetik belirlenimcilik tartışmasında yukarıdaki korkulukları öne sürmek, güncel tartışmayı anlamamıza yardımcı olmaz. Çünkü günümüzde bu tartışmanın tarafı olan bilim insanları ve düşünürler, Davenport tarzı basit açıklamalar öne sürmezler. Kimse, kalıtımsal IQ farklarının, depresyona yatkınlığın veya içe kapanık kişiliğe sahip olmanın, sirke sineğinde göz rengi farklarını açıklayan Mendelci şemayla açıklanacağını iddia etmez. Ayrıca bu tartışmada genetik belirlenimcilik taraftarı sayılanlar, istenmeyen bir genetik özelliğin zorunlu kısırlaştırma veya ötenazi gibi yöntemlerle eradikasyonunu savunmaz.

Genetik belirlenimcilik tartışması, genetik farkların genomun bütününden veya genetik olmayan gelişimsel etkenlerden *bağımsız* birer neden sayılıp sayılamayacağı tartışmasına evrilmiştir. Artık temel sorun, genotipin davranışsal fenotipleri etkileyip etkilemediği tartışmasından ziyade gelişimsel bir sistem içinde genetik farkların nedensel etkilerini belirleme problemidir. Eski çevre/gen karşıtlığının bu noktaya evrilmesinin bir nedeni popülasyon düzeyinde neredeyse her davranışsal farkın kısmen genetik olduğunun keşfedilmesi olduğu kadar genetik farkların da çevresel farklarla etkileştiğinin öğrenilmesidir.

Bu problemin modern genetik literatüründe en can yakıcı biçimde kendini hissettirdiği alan genom düzeyinde bağlantı analizi çalışmalarıdır (İng.= GWAS). Bu çalışmalarda amaç, bir hastalık veya herhangi bir fenotipik çeşitlilik türünün genomun bütününde gözlenen nükleotid çeşitliliğiyle ilişkilendirilmesidir. Bu çalışmaların sonuçlarından biri, yaygın hastalıklar veya davranışsal farkların çok sayıda genetik farkla ilişkili olmasıdır. Bir diğer sonuç ise, genetik varyasyonun, eski biyometrik yöntemlerle ölçülen kalıtımsallık derecesinden çok daha düşük çıkmasıdır. Yani bu çalışmalarla varyasyonu etkileyen birçok genetik bölge bulunur, ama bunlar kalıtımsal varyasyonu açıklamaya yetmez. Son söylediğimize teknik terminolojide kayıp kalıtımsallık problemi adı verilir. Kayıp kalıtımsallık problemini, daha çok genetik varyantı dahil ederek çözmek kayda değer bir seçenek ise de temel sorun, genetik nedensellikle ilgili gibi görünmektedir.

Her faktörün düşük etkiye sahip olduğu, ama toplamda etkinin büyük olduğu sistemler, etkileşimli sistemlerdir ve bu tür sistemlerde tikel faktörlerin etkilerini ayırt etme problemi genetiğe özgü bir problem değildir. Deneysel olmayan tüm bilimler ve özellikle toplum bilimleri bu problemle uzun süredir uğraşmaktadır. İstatistiksel yöntemler, yoksulluk gibi genel faktörlerin kimi davranşsal bozukluklar üzerinde büyük etkileri olduğunu göstermiş olsalar bile yoksulluğun hangi bileşenlerinin hangi etkileri olduğunu göstermekte yetersizdirler. Benzer biçimde davranış genetiğinin ikiz ve evlat edinme çalışmaları genlerin bazı davranışsal özelliklerde çok etkili olduğunu göstermelerine rağmen bunların genetik temellerine nokta atışı yapmak

şimdilik mümkün değildir. Kayıp kalıtımsallık problemi karmaşık bir fenomenin tikel nedenlerini ayırt etme probleminin bir yansımasıdır. Bu tür problemlerle uğraşan bir bilimi geçtiğimiz yüzyılın "belirlenimcilik" anlayışıyla eşitlemek gerçeği çarpıtmaktır. Ancak, inceltilmiş, dolaylı bir genetik belirlenimcilik türünün genetik araştırmaya damga vurduğunu söylemek

Gen merkezci biyolojik araştırma tarzı, bu tür problemlerle karşılaşıldığında hemen terk edilecek bir paradigma olmadığını geçtiğimiz yüzyılda kanıtladı. Ekonomik ve biyolojik açıdan önemli neredeyse hiçbir biyolojik özellik - ineklerde süt verimi, ağırlık, boy, böceklerde ilaca bağışıklık, sirke sineklerinde kanat şekli, insanda genel zeka faktörü - basit bir Mendelci kalıtım yolu izlemiyordu ama bu Mendel genetiğinin ilerleyici bir araştırma programı olmasını engellememişti.

Lakatos'un terminolojisini ödünç alırsak, genetik bilimi doğumundan itibaren bir anomaliler denizinin içinde yüzüyordu. Ama anomaliler, Mendelci açıklamayı revize ederek kapsanabiliyordu. Tek faktör yetmediğinde, bir özelliği bir çok faktörün etkilediğini söylemek mümkündü. Çok faktörlü kalıtım görüşü, Imre Lakatos'un hem pozitif höristik hem de negatif höristik kavramlarını aynı anda karşılıyordu. Hem genlerin aktarım ve zigot oluşumu sırasında saf kaldıklarını, yani Mendel genetiğinin temelinin güvende olduğunu göstermek, hem de karmaşık kalıtım düzeni gösteren özelliklerin Mendelci çerçevede açıklanabilmesini sağlamak açısından çok faktörlü kalıtım görüşü pozitif ve negatif höristik kavramlarının işlevlerini yerine getirir. Mendelci oranlardan bir sapma olan bağlantı fenomeni, Mendel genetiğinde bir araç haline getirilmiş, genlerin kromozomlar üzerindeki pozisyonlarını haritalamayı mümkün kılmıştı. Sapmaların yeni yöntemler doğurması ve bu yöntemlerin genetiğin kuramsal yapısını revize etmesi genetik tarihinde bir kuraldır.

Benzer bir tabloyu, moleküler biyolojinin ilerleyişinde de görürüz. Genetik enformasyon kavramı, öncelikle protein yapılarının statik, kalıtımsal kaynağını tanımlarken sonra metabolizmanın dinamik yönünü de kapsayacak biçimde genişlemişti. Ökaryot genetiğinin karmaşıklığı, gen merkezciliği ve enformasyon kavramını ortadan kaldırmadı ama esnetti.

Bu esnemenin belirgin örneklerinden biri, gen kavramının kendinde yaşandı. Moleküler biyolojinin doğuşunda protein kodlamakla tanımlanan gen, artık protein kodlamayan DNA bölgelerini de kapsıyor. Genetik program, eskiden açık seçik, düzenli bir komut dizisi olarak görülürken artık paralel olarak işleyen, komutlar ve veri arasında zikzaklar çizen düzensiz bir yapı olarak görülüyor.

Aslında tüm bu değişimler, genotip ile fenotip arasındaki karmaşık ilişkiyi, eski güzel günlerdeki gibi kutsal DNA molekülüne haritalama isteğinden kaynaklanıyor. Canlılık, genetik enformasyon çuvalına sığmıyor, çuval revize ediliyor. Tüm bu aksaklıklara rağmen gen merkezcilik neden biyolojiye halen egemendir? Bunun hem metodolojik, hem ampirik, hem de tarihsel nedenleri var. Ampirik nedenlerden en önemlisi, DNA yoluyla kalıtımın en güvenilir kalıtım sistemi olmasıdır. Metodolojik nedenlerden en önemlisi DNA'nın canlı ile ilgili statik, kolayca erişilebilir bir veri kaynağı olması ve DNA'ya müdahale ederek biyolojik süreçlere nasıl müdahale edeceğimiz konusunda bilgi birikimimizin zenginliğidir. Tarihsel neden ise son söylenen ile çok yakından ilgilidir. Genetiğin yüz yıllık tarihinde elde edilen birikim, canlılara taze bir bakış geliştirmemizi engelliyor.

Üç neden kümesini birleştirdiğimizde şöyle bir tablo ortaya çıkıyor: DNA temelli kalıtımın biyolojiye egemen olması, DNA'nın biyolojik süreçlerdeki merkezi rolünden kaynaklanıyordu, yani rastlantısal değildi. Ancak belirli türde bir nesneyle ve belirli yöntemlerle uzun süre haşır neşir olmak, bu nesnenin önemi konusunda yanlı fikirler oluşmasına neden oldu. Biyolojinin ve ilgili alanların neredeyse tüm araştırma araçları gen merkezci bir pratik etrafında organize edildiği için gen merkezcilik egemen olmayı sürdürüyor. İşte bu yüzden, enformasyon kavramının metafiziği, biyolojik açıklamadaki yetersizliği ve kavramda yapılan *ad hoc* revizyonlar, gen merkezciliğin neden halen egemen olduğunu açıklamakta ikincil önemdedir.