Raphael Falk

Genetic Analysis

A History of Genetic Thinking

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There is a paradox lying at the heart of the study of heredity. To understand the ways in which features are passed on from one generation to the next, we have to dig deeper and deeper into the ultimate nature of things – from organisms, to genes, to molecules. And yet as we do this, increasingly we find we are out of focus with our subjects. What has any of this to do with the living, breathing organisms with which we started? Organisms are living. Molecules are not. How do we relate one to the other?

In *Genetic Analysis*, one of the most important empirical scientists in the field in the twentieth century attempts, through a study of history and drawing on his own vast experience as a practitioner, to face this paradox head-on. His book offers a deep and innovative understanding of our ways of thinking about heredity.

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Genetic Analysis

A History of Genetic Thinking

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Is the growth of science essentially so slow and so continuous that our attention is attracted only by the sudden showy change, which, like the bursting of a chrysalis, is merely the sequel to something of more importance which went before? Or, does a particular piece of work . . . have a value per se *which transcends the others completely? Probably both questions should have affirmative answers.*

<div align="right">

(East, 1923, 227)

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Acknowledgments

uncompromising analysis has always been for me a beacon to strive to follow.

I wish to thank them all, and the many whom I did not mention by name, for their help in bringing to fruition this attempt to evaluate the role of genetic analysis in the intellectual context of contemporary life sciences.

Introduction

The subject of this book is genetic analysis. I have been involved in genetic analysis for over a half century, first in active experimental research and later doing research on the history and philosophy of genetics.

In 1965, the centenary of Mendel's presentation to the Natural History Society in Brno, two books were published with almost identical titles by two leading geneticists of that time: Alfred H. Sturtevant's *A History of Genetics* (1965) and Leslie C. Dunn's *A Short History of Genetics* (1965). Sturtevant's preface was very brief and succinct: "The publication of Mendel's paper of 1866 is the outstanding event in the history of genetics; but . . . the paper was overlooked until 1900, when it was found. Its importance was then at once widely recognized. These facts make the selection of topics for the early chapters of this book almost automatic" (Sturtevant, 1965, vii). I will discuss this notion at some length in later chapters. Dunn's approach was more reflective; he focused on the role and significance of the history of science. With respect to the history of genetics, Dunn noted:

> One of the interesting things about the history of genetics is that a few relatively simple ideas, stated clearly and tested by easily comprehended breeding experiments brought about a fundamental transformation of views about heredity, reproduction, evolution and the structure of living matter. It was chiefly the elucidation of the theory of the gene and its extension to the physical basis of heredity and to the causes of evolutionary changes in populations which gave genetics its unified character.
>
> Dunn (1965, vii)

Nonetheless, despite the magnitude of the achievement, Dunn observed that there was no interest in the history of genetics among historians of science because "[t]he events leading to its rise have been too recent to

attract the interest of professional historians" (Dunn, 1965, ix). And
the same was true of researchers who were practicing genetics. In the
introduction to his book Dunn noted his surprise when a fellow geneticist
explained why he was not familiar with the work of a predecessor: "if I
read everyone else's paper, I wouldn't get my own written." Dunn noted
that "an adequate perspective is an essential element in all historical
research. [But f]or those who have participated in the development of
genetics, the interest in the unfolding facts and theories and the oppor-
tunity to influence its surging progress have in general outweighed any
temptation to stand aside long enough to reflect on the origin of its
ideas and where they were leading." He agreed that "this on the whole is
as it should be" (Dunn, 1965, ix), but commented that although "that
attitude . . . is not a useful view for science generally . . . it is under-
standable in a field like genetics, where liberation from restrictions
imposed by traditional ideas is sometimes a necessary condition for
developing new views." And he stressed that "this aspect of genetics is
especially marked today [1965]" when

> the attention of both the scientific and the lay public has for the past ten
> years been focused on the molecular basis of heredity and on the mode of
> transmission and transcription of a code of instructions which guides
> progeny in repeating the biological patterns of their ancestors. The dis-
> coveries in this field have been so rapid and exciting and so recent as to
> create an impression that genetics began in 1944 with O. T. Avery's dis-
> covery that the nucleic acid DNA is the vehicle of hereditary transmission.
>
> Dunn (1965, xii)

Dunn referred to the book of Alfred Barthelmess of 1952 that repre-
sented "the first attempt to trace the origin and path of development of
the science of heredity."

> Whether one places the date of the birth of this branch of biology in the
> year 1900 or 1866 or even farther back, it nevertheless remains astonishing
> that until now no history of it has been written. The science of heredity has
> unfolded itself so precipitately and flowers today so vigorously that one
> could easily think, in seeking a reason for this lack, that there has been no
> time for reflection.
>
> Dunn (1965, xv)

The situation has changed radically since then. The history and the
philosophy of genetics have attracted a great deal of attention by his-
torians and philosophers of science (e.g., Harman, 2004; Keller, 2000;

Kohler, 1994; Moss, 2003; Olby, 1985; Orel, 1996), and to a more modest extent by scientists themselves (e.g., Carlson, 1966 /1989, 2004; Falk, 1986; Glass, 1963; Lederberg, 1990; Portin, 1993; Zuckerman and Lederberg, 1986). Special attention has been devoted to the history of genetics in the molecular era (e.g., Holmes, 2001; Judson, 1979; Kay, 2000; Morange, 1994, 1998; Olby, 1974; Rheinberger, 1997; Watson, 1968; Weiner, 1999). Many modern texts have claimed that a break in the continuity of genetic theories occurred in the 1950s with the introduction of the Watson–Crick model of DNA, the establishment of experimental research at the bacterial level, and the introduction of molecular meth-odologies to genetic analysis (see Olby, 1990, for a discussion). Thus philosopher Philip Kitcher has suggested: "There are two recent theories which have addressed the phenomena of heredity. One, *classical genetics*, stemming from the studies of T. H. Morgan, his colleagues and students, is the successful outgrowth of the Mendelian theory of heredity redis-covered at the beginning of this century. The other, *molecular genetics*, descends from the work of Watson and Crick" (Kitcher, 1984, 337). Of considerable influence has been Evelyn Fox Keller's thesis that the change from a linear mode of thinking to that of a cybernetic, informa-tional mode changed the image of the gene from that of an *acting* agent to that of an *activated* agent (Keller, 1995, 2000, 2002). Moreover, Lenny Moss suggested that the gene concept should be dichotomized into a gene-*P* which is identified by a phenotypic marker and a gene-*D* which is defined by its molecular sequence (Moss, 2003).

I claim that it is wrong to conceive of the phenomena of heredity as involving two theories, classical genetics and molecular genetics. There are not two theories one of which (classical) should be reduced to the other (molecular). Indeed, philosophers of science have shown that formally such a reduction is futile (e.g., Kitcher, 1984; Schaffner, 1976. See also Sarkar, 1998). I propose that it is more meaningful historically and more helpful scientifically to view these not as two theories, but as one continuous theory that deals with the same array of problems at different levels of resolution. In the biological sciences, claims of regu-larity (and "lawfulness") are contingent on past events that happen to have taken place and were (nearly) fixed by natural selection and by the constraints of structure and function that have prevailed. In the physical sciences, foundational laws involving the nature of matter have been found to be essentially ahistoric – that is, time-translation-invariant over time scales close to the age of our universe. As Dobzhansky famously stated: "Nothing in biology makes sense except in the light of evolution"

(Dobzhansky, 1973), or, in the words of a philosopher of science: "the aim of biological theorizing is not, as it is in physical science, the identification of natural laws of successive generality, precision, and power, but the sharpening of tools for interacting with the biosphere" (Rosenberg, 1979, 254).

This book is an argument against a conceptual discontinuity between "classical" and "molecular" theories of genetics. In it I claim that molecular genetics is an organic extension of the so-called "classical" conceptions of genetic analysis, an evolution by refinement of methods, for example adopting biochemical and molecular markers (and eventually simply specific nucleotide bases, SNPs) to replace the traditional phenomenological markers such as wrinkled pea seeds or white eye-color of flies. Genetic analysis is the art of analyzing the phenomena of heredity by hybridization. Hybridization is a very ancient art, practiced primarily by breeders. The science of heredity is based on this ancient art: starting with Linnæus in the eighteenth century this art became a research tradition. Defined this way, the tradition is based on a methodology of interfering. Experimental examination of (preconceived) theories should be viewed as parallel to what I call the morphogenist tradition, which relies mainly on observations in the field and on the dissecting table. Although hybridization nowadays incorporates a wide array of techniques, including many at the level of DNA molecules, since 1865 the art has developed as an integral and consistent discipline on the foundation of Gregor Mendel's experiments with hybrids of garden peas. In the 1940s, the aggressive developments of what many view as a new research tradition of molecular biology began to increasingly affect not only the practical application of molecular methodologies to genetic problems, but also the conceptualization of the issues of genetics, to the extent that molecular genetics was claimed to comprise a discipline distinct from classical genetics.

Genetic Analysis presents the study of inheritance as a *conception directed by a methodology*. As such the book is organized as a historical study of the design of experimental evidence and its application to genetic theories.

As the art of analyzing the phenomena of heredity in the tradition of hybridization, genetic analysis is a discipline characterized by *methodological reductionism*, the assumption that empirically following single variables is the effective way to bridge realms. *Conceptual reductionism*, on the other hand, assumes that phenomena may be determined by a component or components from a more basic realm, and that the

component or components individually or interactively bridge the phenomena to a higher realm. Methodological reductionism may be considered an epistemological statement, whereas conceptual reductionism is essentially an ontological one (see Sarkar, 1998, 19ff.). The distinction is one between explanation and resolution (see Falk, 2006, 219). Once we accept this, the problem of a formal, classic attempt to reduce one theory to the other – problematic as this by itself may be – becomes irrelevant to genetic analysis (see Fuerst, 1982).

In the introduction to his *Short History of Genetics* Dunn confessed that what interested him most in the history of science was "the relationship between ideas held at different times, couched in similar terms, yet obviously having different contents and meanings . . . What, if anything, does the second concept owe to the first? How, if not derived from the first, did the second arise?" (Dunn, 1965, xvii). Once we overcome the issue of the formal conceptual reduction of theories, we may, as Dunn suggested, trace the evolutionary change in the meaning of concepts. The understanding of this evolution of concepts is significant not only to the historian or the philosopher of science; it should also be of primary interest to the practicing geneticist.

Consider the concept of the gene: When practicing geneticists involved in deciphering the human genome at the turn of the millennium officially bet on the number of genes of the human genome, what were they referring to? Certainly not the concept formulated by Johannsen, in 1909 nor the dictum of "one gene – one enzyme" formulated by Beadle and Tatum in 1942. In 2003–4 at a workshop on "representing genes," organized by Karola Stotz and Paul Griffiths at the University of Pittsburgh, participants discussed roughly a dozen descriptions of generating transcripts and/or polypeptides that were considered to be genes. Why is the polypeptide translated on the ribosomes less of a phenotype than the vermilion eye-color of a Drosophila fly? Or for that matter, would it be wrong to refer to the transcribed RNA molecule (before splicing or afterwards) or even to the DNA sequence itself as phenotypes of the "something" that is conceived as the genotype? Aren't we actually reading off the genotype directly from the DNA sequence "this most basic of all phenotypes"? (Griffiths, Gelbart, Miller, and Lewontin, 1999, 576). A recent TV program claimed: "Tell me your genes and I'll tell you who you are." Having been trained as an experimental scientist I examine my claims empirically. The issue of whether the concepts of genetics have changed continuously or whether fundamentally different concepts have been generated at different periods is an issue that should

be examined by juxtaposing the experiments done and quoting from the discussions of the researchers involved and the textbooks of the time. This I wish to do in the present book.

Mendel did not introduce a Kuhnian paradigm shift in biological research with his paper of 1866. Rather his work was profoundly integrated in the social, religious and scientific tradition of his Central European community. Acting within the hybridist research tradition, Mendel believed in a world constructed from the bottom up on the basis of God-directed lawfulness that had to be discovered and explicated. In that sense Mendel's ideas relied conceptually and therefore also methodologically on notions of the physical sciences using numerical analyses. His experiments were reductionist, bottom-up examinations of his theories based on his beliefs. This contrasted with the traditional top-down morphogenist research methods employed in comparative anatomy, embryology, or natural history, which viewed life as being a property that emerged *per se*, and was not (or not necessarily) reducible to simple phenomena that could be analyzed numerically in terms of physical science.

In 1900, Mendel's work was "rediscovered" only in the sense that researchers – foremost among them William Bateson and Hugo de Vries – had encountered difficulties with the evolutionary morphogenist tradition, whether in field observations or at the embryologist's and cytologist's laboratory bench, and had tried to overcome these by imposing the heuristics of the hybridist tradition onto their morphogenist conceptions. I suggest that when genetics was established as a discipline of the life sciences at the beginning of the twentieth century it was on the basis of an attempt to reconcile the two research traditions. However, the result was that genetics became a discipline of confrontation between material hypothetical constructs and instrumental intervening variables (Mac-Corquodale and Meehl, 1948) rather than a discipline of a reductionist research heuristics that formulated its regularities in lawful terms. A focal point of this confrontation was when R. A. Fisher (1936) challenged the experimental data in Mendel's paper, asking "Has Mendel's work been rediscovered?" Many years later Robert Olby would reformulate the question by asking "Mendel no Mendelian?" (Olby, 1979). For Mendel and for Wilhelm Johannsen – who introduced the genotype and gene conceptions – the hereditary factors were only *a priori* helpful instrumental variables, while for R. A. Fisher they were experimental material constructs. The "too good" fit of data and expectations led to

suspicion of Mendel's findings or the actions of some of his associates rather than acceptance of his findings as evidence of a well-designed experiment of a preconceived theory (see, e.g., Sapp, 1990, chapter 5, 104–119).

With the adoption of the chromosome theory of inheritance by Thomas H. Morgan and his associates in the 1910s, genetics achieved its independence as a research discipline. It adopted the analytic reductionist research heuristics but maintained a dialectical conceptual confrontation between materialists and instrumentalists, or equivalently, between those who believed that they were dealing with hypothetical constructs and those who insisted that their entities were nothing but intervening variables. The evolution of the concept of the gene reflects this methodologically based conceptual tension as an ongoing dialectical confrontation between instrumental and material entities (Falk, 1986, 2000b, 2004).

Genetic analysis was inherently a phenomenological research discipline. Mendel used variables that were experimentally discernible and adequate for gathering considerable data to represent his *Faktoren*, irrespective of what their specific properties were. Once Johannsen overcame the identification of the Mendelian factors with "unit characters," the observable characteristics served only as "markers" of the genes. The chromosome theory of inheritance provided a firm cytological basis for the Mendelian analysis, and the analytic genetic linkage theory provided strong support for the cytological observations. The improvement in the sophistication of the phenomenological reductionist research methods turned the balance increasingly toward material "genocentrist" determinism, and genetic research increasingly introduced biochemical, even molecular, marker-variables instead of the classic phenomenological variables. Reductionist determinism triumphed with the evidence for DNA being the material basis of genetic claims and Watson and Crick's presentation of the model of the complementary double helix in 1953. Fungal and microbial screening methods increased the resolving power of genetic analysis by many orders of magnitude, and within a decade phenomenological genetics turned into molecular genetics. Reductionist genetic analysis reached a new peak with the acceptance of Crick's Central Dogma of genetics in the late 1950s: Genetic specificity is maintained by the sequence of bases in the DNA and expressed in the corresponding colinearity of the sequence of the amino acids of the polypeptides; DNA determines RNA which informs proteins. What was true for *E. coli* would be true for the elephant. Indeed, the triumph of methodological reduction was conceived as the victory of conceptual

reduction (Monod, 1972), to the extent that some philosophically minded researchers believed that the science had exhausted itself, and no more fundamental principles of living organisms could be discovered (see Stent, 1969).

This picture started to change in the mid-1960s when inconsistencies arose within reductionist molecular genetic analyses. The more the reductionist heuristic of molecular analysis progressed, the more it became obvious that conceptual reductionism must be modified, and researchers returned to a conception of top-down systems. As it turned out, the simplistic reduction of genes to DNA sequences collapsed when it appeared that not all DNA was "genetic" – terms like "redundant" and even "junk" DNA prevailed. Even more traumatic was the increasing evidence that DNA sequences were not "simply" and unequivocally transcribed into messenger-RNA, which is straightforwardly translated into polypeptides. It became recognized that DNA sequences were also involved in "regulation" rather than merely in "coding," and it became increasingly clear that it was the cell (if not the organism) – rather than DNA, or even DNA transcribed into RNA that is translated to a poly-peptide – that was the critical *sub-system*. Conceptually, it was the per-spective of the system that had to be clarified.

Even though researchers were aware that biological systems must be conceived as such, they were restricted by complexity because of lim-itations on human computational and cognitive powers, and there was often an irresistible temptation to continue to extend the efficient reductionist heuristics to reductionist conceptions. However, with the increasing computational power of modern computers and the parallel development of the computational sciences in capacities such as modeling and simulation, some of these human cognitive limitations were overcome. The triumph of the Human Genome Project at the turn of the millennium was proof of this expansion of technology and its power to affect theory. Once this conceptual top-down perspective was imposed on the bottom-up experimental heuristics, "genetic analysis" became less genetic. Biochemistry, cell biology, embryology and devel-opment, evolution, even comparative taxonomy, all became players in "system analysis," which transformed the life sciences. Today there is no longer a distinct science of genetics; neither neurobiologists nor medical doctors can avoid the involvement of genes in their research and prac-tice. Yet, genetic analysis as a research method prevails, and now two DNA strands from organisms as distant as a mosquito fly and a Mangrove tree may be the ones that are hybridized *in vitro*.

When I was an undergraduate, professor Georg Haas at the Department of Zoology of the Hebrew University used to complain in his comparative anatomy class that he was unable "to talk as an orchestra": He was reduced to linearly and sequentially presenting processes that occurred simultaneously and interactively. I too am restricted by this limitation and must present my evidence successively, but I hope to convey the reality of interactive integration by occasionally telling the same story from a different angle. As may have become clear, my belief in the intellectual continuity of genetic analysis makes my story rather "Whiggish" in spite of my attempts to stress the incessant emergence of new ideas and notions along a continuous road. I present in some detail not only experiments that I consider to be pivotal for genetic analysis but also some that serve to illuminate specific issues of genetic analysis, by giving both the rationale of the experiments and the methodology chosen to answer the challenge, often with quotations from the original sources. Admittedly, the presentation of the experimental evidence is heavily biased towards Drosophila, since this was the main object of my research work.

Each part of this book introduces a central idea of genetic analysis and comprises chapters that give the experimental and theoretical evidence for that central idea.

Part I "From Reproduction and Generation to Heredity" discusses the significance of Linnæus and his followers, who established a *science* of heredity. It recounts the role of Mendel in establishing the parameters of genetic analysis by the design of his experiments.

In Part II on "*Faktoren* in Search of Meaning" I discuss the intellectual circumstances surrounding the acceptance of the Mendelian principles, the constraints of evolutionary and cell biology and the establishment of the foundations of an independent discipline when these constraints were overcome.

Part III is devoted to "The Chromosome Theory of Inheritance," the development of new instruments of analysis, including the establishment of analytic cytogenetic research.

Part IV explains the concept of the gene. It describes the confrontation between the instrumental and the material conception and discusses the concept of the gene at the heart of genetics as a reductionist science.

After introducing the emerging genetic analysis research tradition in the earlier parts of the book, in the later parts I shift towards describing the expansion of this research tradition to the level of molecular research.

Part V, "Increasing Resolving Power," is devoted to the expansion of genetic analysis with the establishment of the details of the material basis of heredity. This increase in the resolving power of the analysis was enabled by a transition in study from eukaryotes to bacteria and from phenomenological markers to biochemical and eventually molecular markers. I also discuss the arguments for and against the conception of a molecular biology theory (or research program) comprising distinct theories of "classical" and "molecular" genetics.

Part VI discusses the experimental evidence of gene function and its dependence on the cellular system that turns the nucleotide sequence into one component of gene function rather than its determinant.

In Part VII I discuss the breakdown of the reductionist conception together with the elaboration of reductionist molecular methodologies, the return of the top-down systems analysis to genetics research and the realization that the elephant is not a large-scale *E. coli*, which culminated when genetic research expanded into all disciplines of the life sciences. Genetic analysis became an integral part of the new biology of the genomic age, and maintains its role in the study of the development of the individual organism and in the dynamics of evolution.

In the concluding remarks, I suggest that the triumph of genetics in the genomic (and post-genomic) era is precisely in its maintaining the dialectics of adopting bottom-up methods and heuristics in resolving top-down analyses of organisms as systems.

I

From reproduction and generation to heredity

> And Adam lived thirty and a hundred years, and begot a son
> in his own likeness, after his image.
>
> <div align="right">Genesis 5, 3</div>

To beget a son in one's own image was considered an attribute of reproduction and generation. In biblical times, inheritance referred to the transmission of material commodities or land-ownership from one person to another:

> And Abraham said, Lord God, what wilt thou give me, seeing I go child-less, and the steward of my house is this Eliezer of Damascus? . . . And behold, the word of the Lord came unto him saying, this shall not be thine heir; but he that shall come forth out of thine own bowels shall be thine heir.
>
> <div align="right">Genesis 15, 2–5</div>

Although inheritance also extended to the succession of titles and rights, it only rarely referred to the transmission of the natural traits of living creatures. Eventually, however, inheritance acquired more meta-phoric connotations: "What must I do to inherit eternal life" (Mark 10, 17; Luke 10, 25 and 18, 18).

In Greek philosophy biological continuity was acknowledged as early as the fifth century BC in the *Iliad*, where the metaphoric inheritance of the heroic qualities of the father by the son was taken for granted. And in Euripides' *Electra* the continuity of traits by descendants is alluded to when a servant, finding a lock of hair, attempts to identify Orestes by its resemblance to his sister's hair.

In the Roman Empire inheritance of property was encoded in a voluminous set of laws. The term *Hērēdĭtās* referred to the successor of

the rights and liabilities of a deceased person, or to a successor to a throne. It was also used metaphorically, to describe transmission of characteristics such as glory, hatred, or eagerness. However, when the Romans related to breeding practices in agriculture they referred to transmission by reproduction (Sirks and Zirkle, 1964).

Also in the Middle Ages references to biological transmission were made in the context of reproduction and generation: St. Thomas in the thirteenth century alluded to "bodily defects" that are "transmitted by way of origin from parent to child," or "man generates a likeness to himself in kind" (Zirkle, 1945).

At the turn of the sixteenth century Shakespeare used "inherit" repeatedly in various metaphoric contexts:

> Youth, thou bear'st thy father's face; Frank nature, rather curious than in haste, Hath well compos'd thee. Thy father's moral parts Mayst thou inherit too.
>
> *All's Well that Ends Well*, I, ii, 20–22

Although physicians have used the metaphor of "hereditary" to refer to transmission of disease at least since the sixteenth century, it must be kept in mind that diseases were not considered "properties" of living organisms, but rather scourges that *inflicted* the organism.

The terms *reproduction* and *generation* were used to signify biological continuity and change.

The change in the role of the term "heredity" to imply a theory was closely linked to the increasing upheavals in social awareness that followed the discoveries of new continents in the sixteenth and seventeenth centuries. Stephen Toulmin (1972, 41) noted that Captain James Cook's arrival in Tahiti on H.M.S. *Discovery* in 1769 was the beginning of a new era in the recognition of natural diversity. Cook's mission had been to make some astronomical observations for the Royal Society, but on the *Discovery*'s return the voyage became the talk of Europe for quite other reasons. The customs of the Tahitians proved far more intriguing than the astronomical distances of the planets. The scene, however, changed not only with respect to cultural anthropology. The number of new, unknown and unexpected species of animals and plants found on every new voyage caused a profound revolution in the conception of the world of nature and the species that inhabited it.

Taxonomy became a central issue of science and philosophy in the seventeenth century. Two notions of taxonomy of natural systems emerged: One notion conceived of taxonomy as a human device to

control nature's variability using morphological and anatomical observations as its methods. Starting with Buffon's pragmatic classification this morphogenist research tradition was able to perceive and conceive change, and this culminated in the theories of evolution of species of Lamarck and Darwin. The second notion was the diametrically opposing Linnæan taxonomy that conceived of each species as a distinct essential entity given by Nature.

Hybridization was the time-honored tool of animal and plant breeders to defy the given order of Nature and Linnæus and his followers adopted it as the analytic tool of their research tradition. As a breeders' device hybridization was often directed at the transmission of specific traits. This tradition reached its peak in the middle of the nineteenth century when the monk Johann Gregor Mendel combined his notions of the divine lawfulness of nature, the reductionist insights of his university education in physics and mathematics, and the experience he gained from his community of breeders to design the experiments that allowed him to formulate in analytic terms the laws of inheritance.

1

The biologization of inheritance

Similarity and variation among living creatures has long been a mystery that has stimulated the classification and organization of life into hierarchical systems, as well as the induction of the differential ranking of individuals in society. Variation and similarity also provided the material for one of the most basic ancient unfolding developments of human culture, animal and plant breeding. The first chapter of *Genesis* beautifully reflects the ancients' conception of the hierarchical, as well as anthropocentric, catalog of the universe:

> In the beginning God created the heavens and the earth . . . Then God said, "Let the land produce vegetation: seed-bearing plants and trees on the land that bear fruit with seed in it, according to their various kinds." And . . . the land produced vegetation: plants bearing seed according to their kinds and trees bearing fruit with seed in it according to their kinds. . . . And God said, "Let the land produce living creatures according to their kinds: livestock, creatures that move along the ground, and wild animals, each according to its kind." . . . Then God said, "Let us make man in our image, in our likeness, and let them rule over the fish of the sea and the birds of the air, over the livestock, over all the earth, and over all the creatures that move along the ground."
>
> <div align="right">Genesis 1, 1–26</div>

Animals and plants were believed to have been generated by God as distinct kinds at the time of Creation, and it was reproduction that maintained the link of similarity in living creatures. Although creatures were generated "according to their various kinds," kinds were not necessarily conceived to be discontinuous types. A prevailing notion was that God in his goodness filled the world with a continuous, progressive presence of life, from the lowest to the highest, all distinct yet each adjacent to its next neighbor. This unique hierarchical notion of

continuous-but-distinct was known as the *Scala Naturae*, or the Great Chain of Being (Lovejoy, 1936 [1950]). It was a completely static, ahistoric gradation of living forms that was maintained almost undisturbed until it was challenged in the eighteenth century by typological classifications, and finally toppled by nineteenth-century theories of evolution.

In such a static world, *reproduction* denoted repetition of conserved qualities in the processes of embryogenesis, whereas *generation* denoted the creation of new qualities (see Parnas, 2006). Passive conservation as opposed to active creation has been a *leitmotiv* in the history of what we would single out today as biological inheritance. Heredity and inheritance, which had been terms of social relations, were seldom used in biological contexts: in an impressive number of quotations on the beginning of plant hybridization (Zirkle, 1935a) and on the early history of inheritance (Zirkle, 1945), "heredity" and "inheritance" hardly appear to be mentioned as such.[1] But such terms were increasingly used metaphorically in biological contexts.

In the seventeenth century, Descartes' suggestion that living creatures be viewed "bottom up" as machines whose function could be reduced to that of their components, did not gain momentum. Life sciences maintained a distinct "top-down" perspective: the entities of reference were organisms as such, and the structure and function of their parts were the properties of the whole organism. Thus, it was mainly embryogenesis that provided the empirical foundations for the philosophies of reproduction and generation.

The term "development," and even more explicitly its German equivalent *Entwicklung* (and also its Hebrew equivalent התפתחות), denoted the centrality of theories of *preformation* that conceived of embryogenesis in terms of re-production, as a gradual unfolding of preexisting qualities.[2] These were, in essence, theories of *pangenesis* that conceived of the embryo as an unfolding of elements drawn from all parts of the body of the parent(s). Proponents of *epigenesis*, on the other hand, conceived of embryogenesis more in terms of generation. They relied on constraints imposed by specific (largely conserved) conditions in which embryos grew, a view that secured reproduction, but allowed for more flexible embryogenesis than that of the strict unfolding of preformed determinants. This dichotomy in theories to account for the development

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[1] It must be noted, however, that I saw most of the quotations only in the English translation.
[2] *Entwicklung* was also translated as evolution.

of the individual organism – the input of nature *versus* the input of circumstances – was reflected in deliberations of the principles that determine the organization of living beings as taxonomic systems. Does taxonomy represent given structures of nature or does it reflect adaptive constraints of circumstances?

It was only in the first half of the nineteenth century that reductive notions of "bottom-up" explanations of physics and chemistry gained a foothold in the life sciences (see Lenoir, 1982). But by the beginning of the eighteenth century, Platonic *a priori* abstraction notions began to be accepted in the life sciences. Observed variability of individuals was considered to be noise that could blur but not deny the existence of the genuine type, just as the images on the walls of Plato's allegory of the cave were merely shadows of the "real thing." It was then that "heredity" started to acquire the status of an explanatory term *per se*, rather than merely a descriptive metaphor.

The introduction of heredity as an explanatory concept within the dichotomy of Nature *versus* Nurture, as eventually formulated by Francis Galton, explicated one of the elements, Nature, in terms that made it amenable to methods of experimental analysis. However crucial the methodology of "either/or" in the design of an experiment, its radiation back on the conceptual level of the dichotomy is a hurdle that has plagued thinking about heredity ever since.

The duality of heredity *versus* environment is closely related to the attempt to discern "biology" from "sociology" in human affairs. The socio-political upheavals at the end of the eighteenth century and during the French Revolution decisively effected a disjunction between biology and social culture. Biology was introduced as a distinct discipline at about 1800 (see McLaughlin, 2002). Whereas before the French Revolution the term "heredity" was not used in the sense of natural history, after 1830 the metaphor of "hérédité naturelle" became a widely used term (see also Pick, 1989, 133). In England "heredity" was relatively rare in biological texts before the end of the nineteenth century (although Darwin used the word "inheritance"). As noted by Galton in his memoir, "It seems hardly credible now that even the word heredity was then considered fanciful and unusual. I was chaffed by a cultured friend for adopting it from the French" (Galton, 1908, 288). In the first half of the nineteenth century the metaphor of biological inheritance ceased to be a self-evident observational fact of life; it assumed the role of a postulating abstraction, a force (Gayon, 2000) primarily involved in maintaining the types or the essences which singled out specific attributes of systems of

living creatures. The metaphor of inheritance of traits did not disappear from biology even after Wilhelm Johannsen introduced the discrimination of the phenotypic and the genotypic levels, and still is an impediment to the genetic analysis of systems (see Chapter 4).[3]

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NATURAL TAXONOMIES

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During the eighteenth century two notions of taxonomy of natural systems emerged. We may call these *nominalism* (or *instrumentalism*, or *conventionalism*) and *essentialism* (or *realism*), respectively (Amundson, 2006, 32ff.). For nominalists taxonomic categories did not necessarily represent objectively real relationships of natural systems; most were, according to Amundson, "cautious-reality nominalists." They considered taxonomy as primarily a system that represented the needs of researchers, and asserted that insights into the living systems would be gained preferably by morphological, anatomical, and physiological investigations, irrespective of species borders. Although new species were added to taxonomic lists according to need, attention was drawn to the common aspects shared by living systems; nominalists were, as a rule, rather open to notions of change and evolution of species. Essentialists, on the other hand, believed in the fixity of species, each species being a given, well-defined entity, with unique characters. Newly discovered species were merely species previously unknown. Since taxonomy emphasized the essential, specific properties that differentiated existing entities, hybridization – not individuals' characteristics – was the ultimate research tool of the essentialists that determined taxonomic status. I will call the research effort of the former proponents a *morphogenist-evolutionist tradition* and the latter proponents a *hybridist-typologist tradition*.

When Carlos Linnæus introduced in the eighteenth century an essentialist taxonomy based on the characteristics of plants' organs of

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[3] In 1911, Johannsen opened his talk on "The genotype conception of heredity" by noting that "[b]iology has evidently borrowed the terms 'heredity' and 'inheritance' from every-day language . . . The *transmission* of properties . . . from parents to their children, or from more or less remote ancestors to their descendants, has been regarded as the essential point in the discussion of heredity, in biology as in jurisprudence. Here we have nothing to do with the latter. . . . The view of natural inheritance as realized by an act of transmission, viz., the transmission of the parent's (or ancestor's) *personal qualities* to the progeny, is the most naïve and oldest conception of heredity." (Johannsen, 1911, 129).

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reproduction, it laid the ground for a notion of biological inheritance that examined the hybridability of organisms. Georges Louis Leclerc de Buffon, Linnæus' contemporary, suggested a nominalist taxonomy that considered the structures and functions of living creatures, including their utility for men. Although Linnæus himself hardly applied it in his experimental work, he suggested hybridization as the analytic tool for the study of what became inheritance of characteristics in plants and animals. This was in stark contrast to morphogenists, who maintained natural history, comparative anatomy and physiology as the principle research methods of similarity and variation and continued to think of similarity and variation within the framework of the reproduction and generation of organisms as such.

FROM *SYSTEMA NATURAE* TO HYBRIDIZATION

Linnæus endeavored to provide in his *Systema naturae* of 1735 a *methodus naturalis*, a comprehensive botanical system that expressed the "natural" relations of plants and animals. His *essentialist* or *typological* species concept is traceable to its metaphysical and methodological foundations in Aristotelian logic: plants belong to one and the same species inasmuch as their *form* is determined by their specific *essence*. Plants possess their species-specific form by virtue of its overall function, which consists in reproduction tending toward the preservation of the species' essence (Müller-Wille, 1998). For Linnæus the fructification systems of genera were the essences responsible for the existence of biological kinds. Species comprised plant individuals which were related by descent and distinguished from other plants of the genus by a complex of characters or "form" that remained constant no matter what external conditions those plants were subjected to (Ereshefsky, 2001, 200–208). Varieties, in contrast, were believed to result from the action of accidental external, physical factors in the environment. Species were *types* in a strictly rational Platonic hierarchical classification, and we can count as many species now as were created in the beginning. The dogma of the immutability of species met with general acceptance only in the late-eighteenth and early-nineteenth centuries (Zirkle, 1935b, 443). Yet, this strict essentialist typology had already been disturbed in the 1740s when Linnæus was forced to admit that new species could arise through hybridization after God's original creation (Müller-Wille and Orel, 2007, 179–182).

Hybridization – understood as cross-breeding – has its roots since antiquity in the practices of domestication of animal and plant breeders. Notwithstanding, hybrids, natural or induced, were embarrassments to good order. They had a completely separate status in the hierarchy of nature's taxonomy, and for a long time hybrids were rejected as a source of new species. Although mating of unlikes or hybridization had been a common practice of domestication already in pre-biblical times – witness, for example, the relief from the ninth century BC of Assyrian priests pollinating palm florescences (Gray, 1969, 58 and www.bible-origins.net/EzekielsCherubim.html) – hybridization was considered an act that conflicted with natural generation. The word "hybrid" stems probably from the Greek *ύβρις* which means an insult or outrage, especially when the insult is offered to the gods (*hubris*) or the outrage is connected to sex (Zirkle, 1935a, 1). For the Hebrews the mating of unlike types seems to have been a form of bestiality:

> Ye shall keep my statutes. Thou shalt not let thy cattle gender with a diverse kind; thou shalt not sow thy field with mingled seed; neither shall a garment mingled in linen and woolen come upon thee.
>
> Leviticus 19, 19

For Linnæus, who believed that "there are as many species as there were different forms created by the Infinite Being at the beginning," hybrids seemed irrelevant to his taxonomy:

> I distinguish the species of the Almighty Creator which are true from the abnormal varieties of the Gardner: the former I reckon of the highest importance because of their author, the latter I reject because of their authors.
>
> Linnæus, quoted by Olby (1985, 32)

Although hybrids were rejected because of the *laws of generation*, this did not mean that it was impossible for one kind of organism to give birth to another kind of organism, or that two different kinds could give birth to a third, mixed kind of organism (Müller-Wille, 1998). Still, the only experiment that Linnæus performed with hybridization forced him to relinquish his confidence in the constancy of the number of species, though not in the typological conception of natural kinds.

Central to Linnæus' distinction between species and varieties was that plants belonging to one and the same species when brought under the regime of perfectly homogenous external conditions should be identical in all respects. Any trait difference appearing under such circumstances