# 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 opportunity 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 understandable 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 discoveries 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 discovery 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 represented "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 historians 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 methodologies 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 rediscovered 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, informational 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 regularity (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 (MacCorquodale 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 polypeptide – that was the critical *sub-system*. Conceptually, it was the perspective 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 limitations 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 development, 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 practice. 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.