GENERAL INTRODUCTION

If one were to chronicle the great achievements of the science of genetics, which seeks to describe and explain the phenomenon of heredity, such a history would show a science that has transformed the taxonomical and descriptive pursuits, with its vitalist underpinnings, of eighteenth- and nineteenth-century natural historians into the experimental and thoroughly materialist inquiries of twentieth-century research biologists.

This anthology—a selection of *Scientific American* articles together with Gregor Mendel's classic paper—documents and celebrates two seminal insights from which the field of genetic inquiry has grown: one is the synthesist tradition, and the other is the reductionist tradition.

The synthesist tradition of evolutionary studies has its roots in Darwin's theory that natural selection is the major force in the origin and evolution of species.

The reductionist tradition, which has led to identification of DNA as the substance of the gene, and has culminated in the discoveries of molecular biology concerning the structure, replication, recombination, mutation, and expression of DNA, is rooted in Mendel's positing of the gene (or "factor," as he called it) as the determinant specifying the characteristics of an organism.

The readings are meant to provide the students with a resource to complement formal genetic texts. The readings comprise a series of vignettes that capture the essence of significant problems that have characterized the field of genetics; they have been written by researchers who have directly contributed to clarification and/or solution of these problems.

The study of heredity reveals two distinct phenomena demanding explanation: constancy and change. Those familiar with the preoccupations of the pre-Socratic scientist-philosophers will recognize this problem as constituting the central paradox of their age.

Our ancient forebears were more impressed with the order presented by constancy than they were with the chaos suggested by change, and the adage "like begets like" came to have considerable currency. Yet, ancient agricultural and pastoral man consciously exploited hereditary change in plant and animal breeding while depending on hereditary constancy (or near constancy within lineages) for the success of such breeding.

Investigators of the phenomena of heredity prior to Gregor Mendel were fascinated by this problem, and they worked without success to elucidate the rules of heredity that could explain the diverse patterns of constancy and change they observed in their hybridization experiments. Mendel's insights, methods, and classifications of the data gathered from his pea hybridization experiments allowed him to perceive the order that had eluded his prede-

cessors, and thus to elucidate the basic principles of heredity, namely, those of allele segregation and the independent assortment of allelic differences at segregating loci.

Mendel's empirical laws were published in 1865, but it was not until forty years later, when the process of meiosis was thoroughly understood, that his laws came to have a material basis in the chromosome theory of heredity as proposed independently by Walter Stanborough Sutton and Theodor Boveri in 1903.

Thus the process of meiosis provided the explanation of how the parental alleles segregated from one another during germ cell formation, and how segregating loci, when they were located on separate chromosomes (or at least far enough apart on the same chromosome), assorted independently of each other in accordance with Mendel's second law.

Exceptions to Mendel's second law of independent assortment were readily accommodated within the chromosome theory of inheritance by postulating that segregating loci showing an excess transmission of grandparental allele combinations must be located on the same chromosome.

Furthermore, as was so ably demonstrated by Alfred Sturtevant in 1913, the degrees of the linkage between different pairs of segregating loci could be used to generate an unambiguous, internally consistent linear map of a set of loci. Such maps were interpreted as reflections of the physical organization of the chromosomes as linear assemblages of genes.

These insights and discoveries ushered in the classical period of formal genetics, during which geneticists demonstrated the universality of Mendel's laws as modified by the chromosome theory of inheritance. Geneticists collected mutants, constructed genetic maps, and studied chromosome rearrangements. During this period the gene was considered to be no more than a formal element of genetic determination that occupied a specific location on the chromosome. But with the discovery that DNA is the agent of genetic transformation by Oswald Avery, C. M. MacLeod, and M. J. McCarty (1944), and with its identification as the genetic material of a bacterial virus by Alfred D. Hershey and Martha Chase (1952), the concept of the gene was transformed from an element of formal genetic analysis to a palpable entity: now it was amenable to (and deserving of) physical and chemical characterization.

Biochemists had long been interested in the phosphorus-rich acidic compound that had first been isolated from pus and salmon sperm by Johann Miescher in 1868. With the passage of time and expenditure of effort, nucleic acid was further characterized and found to contain four different nitrogenous bases, which Erwin Chargaff observed varied in relative proportions among DNAs derived from different organisms. However, as was to prove of critical importance in the solution by James D. Watson and Francis H. C. Crick of the structure of DNA, Chargaff also discovered in 1950 the now famous "complementarity" rule: despite the variation in base composition, the ratio of adenine to thymine (A:T) and the ratio of guanine to cytosine (G:C) were each always equal to unity.

This work of identifying the chemical nature of the gene culminated in Watson and Crick's proposal (1953) for the structure of DNA. The structure immediately revealed how DNA could replicate with fidelity and encode information in the linear sequence of its nucleotides.

In the meantime, a separate line of endeavor had already established how genes function. In 1940, George W. Beadle and Edward L. Tatum proposed, as a result of their studies of mutants affecting the functioning of various metabolic pathways in the fungus *Neurospora*, that genes must specify the structure of enzymes.

By 1953 it was recognized that the great diversity among proteins could be attributed to the particular sequence of the twenty different amino acids which composed their constituent polypeptide chains. Thus the gene was

visualized as an extensive linear sequence of the four different nitrogenous bases (adenine, thymine, guanine, and cytosine) that in some way determined the amino acid sequence of the polypeptide specified by it.

With the advent of techniques for labeling with radioisotopes and for the separation and isolation of macromolecules and macromolecular complexes from disrupted cells, the question of what entities and processes are involved in the specification of polypeptides by genes could be pursued. Research based on these techniques led to the identification and description, in molecular terms, of the processes involved in replication, transcription, and translation, as well as the "cracking" of the genetic code.

Such a strong analytic approach could not long go without a banner and a following, and so "molecular biologists" came into being with the credo: "It is not sufficient to identify molecular entities involved in a biological process, but the mechanics of that process must be sought in the structures of those participating entities." So powerful was the seductive attraction of their reductionist platform that many scientists broke with their current disciplines to join the molecularists. Those who remained faithful to their original calling, and especially those engaged in trying to understand the complexity of nature as it is manifest in species, populations, and communities, looked upon this spectacle of reductionist enthusiasm with some distaste.

The understanding of the molecular biology of DNA—its structure, replication, mutation, recombination, and expression—provided at one and the same time a material basis for what had once seemed irreconcilable—constancy and change: constancy deriving from the high fidelity of its replication and change arising from mutation and its recombination.

Both Mendelian and molecular genetics have been assimilated into the explication of the Darwinian theory of evolution to give what Ernst Mayr describes as the modern synthesis. Like the problem of constancy and change, theories of evolution and its mechanism through natural selection also date back to the philosophical speculations of the materialist pre-Socratic scientists Anaximander and Empedocles.

One is thus left with the impression that the great problems of nature have enjoyed a remarkable Parmenidean constancy over the millenia, despite the Heraclitian flux of change and progress that appears to characterize the advance of man's intellectual heritage.