Principles of

GENETICS

Second Edition

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Preface

Those investigators in the vanguard are currently advancing the frontiers of genetics with relentless vigor. Their phenomenal progress is at once awe inspiring and problematical to an author of a genetics textbook. This second edition of *Principles of Genetics* has been revised with an acute awareness that many of its revisions may be doomed to be only of historical interest by the time they reach print.

Space considerations have dictated representative rather than exhaustive chapter bibliographies. The glossary which has been added as an appendix takes definitions from within the text and makes them more readily available as references. In the interest of presenting comprehensively updated material, much of the history included in the first edition has been eliminated and some chapters have been combined and shortened.

The present dynamic state of the science of genetics still has its foundation, however, in previously established (though admittedly not immutable) basic tenets. The prime aim of this book continues to be to present these basic principles in their modern context and as a unified whole.

Many colleagues and friends have assisted in the revision of this book for the second edition. To all who have contributed in any way, I express deepest appreciation. I am especially indebted to C. M. Woolf of the University of Utah who read the manuscript and suggested improvements. My colleagues Lois Cox, John R. Simmons, James W. Edwards, Larry L. Cox, and Gwen Haws have rendered valuable assistance. W. S. Boyle has provided a number of excellent photographs. The portraits of geneticists were drawn by Everett Thorpe. Wilma Turpen and Chrystal Christensen typed the manuscript.

Credits for tables, illustrations, and quotations from other publications are given in the legends according to the wishes of the author or publisher. I am indebted to Professor Sir Ronald A. Fisher, Cambridge, and to Messrs. Oliver and Boyd Ltd., Edinburgh, for permission to abridge tables 3 and 4 from their book *Statistical Methods for Research Workers*. Several illustrations have been redrawn from the National Pigeon Association Booklet.

Logan, Utah
January, 1964

ELDON J. GARDNER

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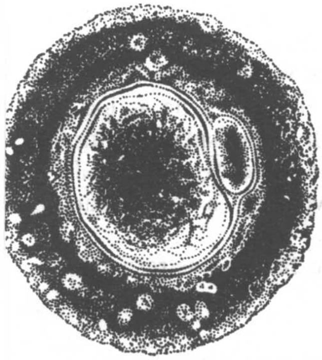

1 The science of genetics

Early observations on plants and animals suggested that underlying natural laws could account for heredity and variation. Investigators trying to unravel the basic principles were unsuccessful, however, until the beginning of the twentieth century, when an adequate scientific foundation was available. By effectively applying the scientific method, many investigators working with various plants and animals accumulated and organized a vast body of facts concerning the mechanisms of heredity and variation. It gradually became obvious that the same basic principles could be applied to plants, animals, and man.

Tigers would beget little tigers and not elephants or representatives of some other species because specific physical elements (genes) were transmitted from parents to offspring through the gametes, that is, eggs and sperm. Pine trees gave rise to other pine trees because their pollen and eggs carried pine-tree information that could be translated into developmental processes which ultimately gave rise to recognizable pine trees. Thus the distinguishing characteristics of a given species were maintained generation after generation.

All characteristics of any organism, however, have hereditary and environmental components, although some traits are more immediately influenced by the environment than are others. Whereas the basic biological pattern is set by heredity, the development of the individual is affected by the environment. Some genes respond differentially to a wide range of conditions. Others are far more precise and restricted in their effects.

GENERAL TECHNIQUES

In exploring the mechanisms of heredity and variation, researchers in the field of genetics necessarily utilize many techniques. The direct approach, through experimental breeding, is widely used whenever possible. In human genetics, however, methods such as studies of twins, pedigree analyses, and statistical procedures are more applicable. Cytological investigation of the cell and its parts is practiced to a limited extent on human material and extensively among experimental animals and plants. On an even more fundamental level, researchers are using biochemical and biophysical techniques in trying to discover and delineate what the gene is and how it functions. Because these techniques are basic to genetics they warrant preliminary consideration at this point.

Experimental Breeding

When an investigator is free to choose his experimental material, he generally tries to make sure it fulfills at least four critical conditions: (1) has a short life cycle, (2) produces abundant progeny, (3) incorporates a large amount of variability, and (4) is convenient to maintain.

Although the same basic principles, at least as far as they concern gene action, seem to apply to all organisms, the investigator most often chooses a material that lends itself well to a particular investigation.

Mice (Fig. 1.1) are favored as research

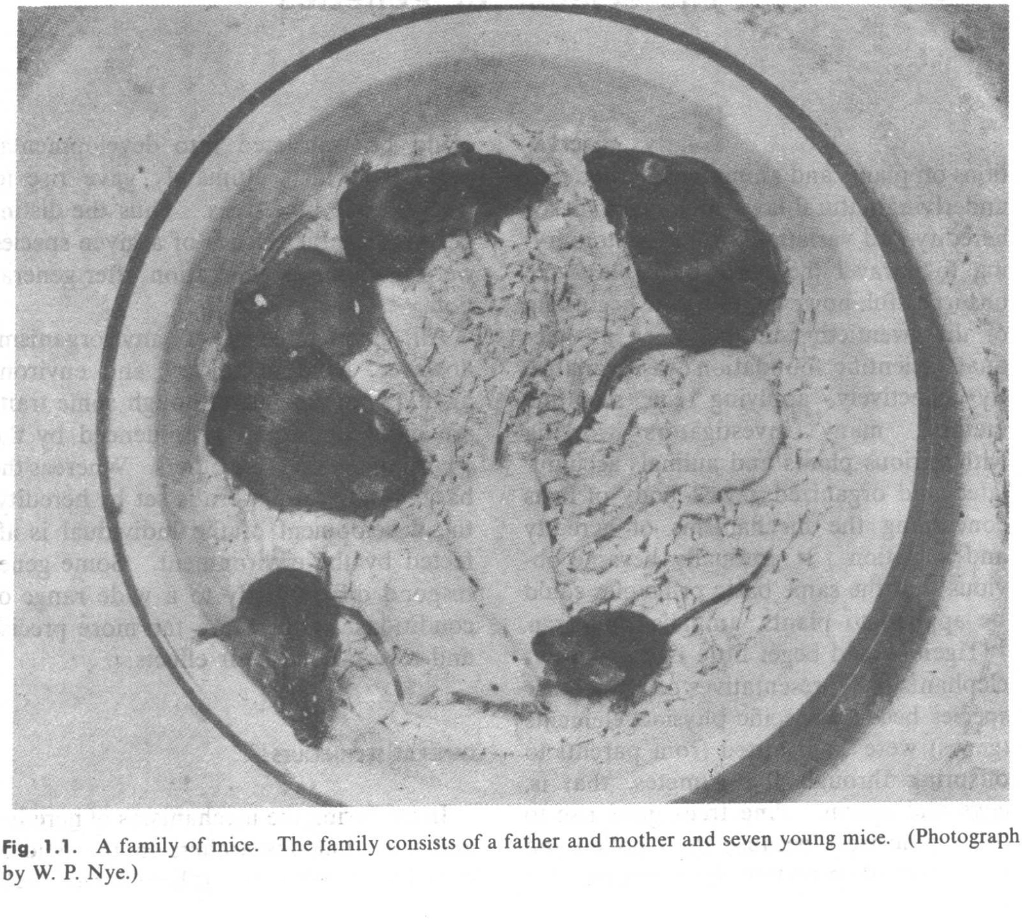

Fig. 1.1. A family of mice. The family consists of a father and mother and seven young mice. (Photograph by W. P. Nye.)

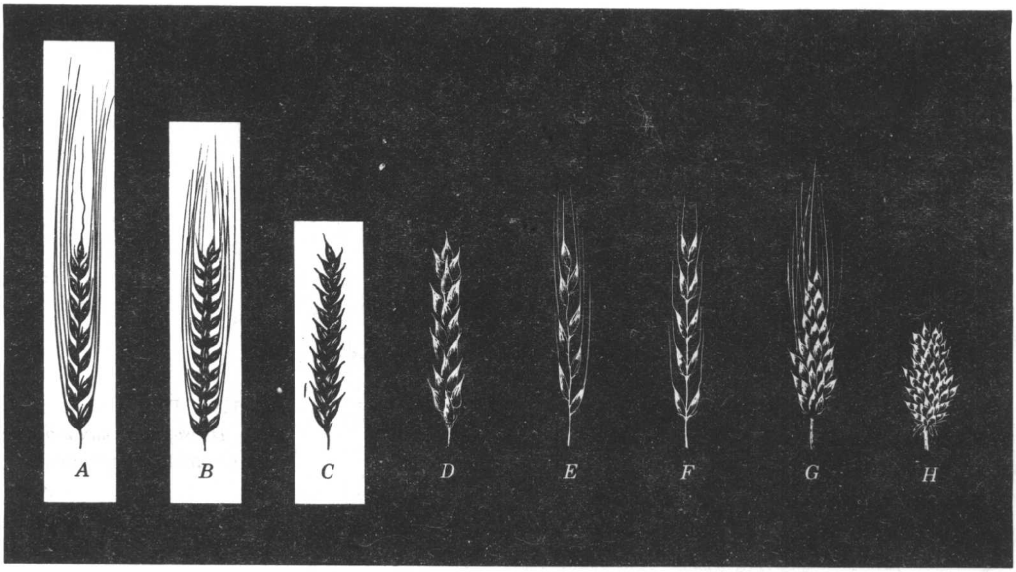

Fig. 1.2. Variations in barley heads. *A*, black, two-rowed, awned; *B*, black, six-rowed, awned; *C*, black, two-rowed, hooded; *D*, yellow, six-rowed, hooded; *E*, yellow, two-rowed, awned, kernels alternate; *F*, yellow, two-rowed, awned, kernels opposite; *G*, yellow, clustered, awned; *H*, yellow, extreme clustered.

subjects because they require only about 2½ months between generations, and their patterns of structure and reaction can be readily observed. Insects, molds, and bacteria are useful because they have short life cycles, abundant progeny, and other favorable characteristics.

Different expressions of a trait in a population (variability) are necessary for genetical analysis. The barley plant is represented by many strains showing considerable variation, and as a result has been widely used in genetic investigations. Some variations in barley heads which depend on single gene differences are shown in Fig. 1.2.

The "vinegar" fly, particularly *Drosophila melanogaster* (Fig. 1.3), is used extensively by genetics students and research workers. Geneticists commonly call this insect a "fruit" fly, but entomologists use the term for another group of flies. Drosophila has been and perhaps now is the most widely used single material for original investigations and learning exercises for genetics students. With the present emphasis on population genetics and evolution, Drosophila promises to occupy a place of even greater importance in the genetics laboratories and field studies of the future.

The bread mold, particularly *Neurospora crassa* (Fig. 1.4), is comparatively simple and lends itself to studies of gene action. Numerous gene changes have been discovered which influence the ability of the organism to produce certain amino acids, vitamins, and other nutritive substances. These findings have led to the discovery of some biochemical steps between genes and traits (Chapter 10). The life cycle of the mold (Chapter 4) includes a sexual and an asexual phase, making the organism suitable for a variety of breeding experiments, some of which are described in later chapters.

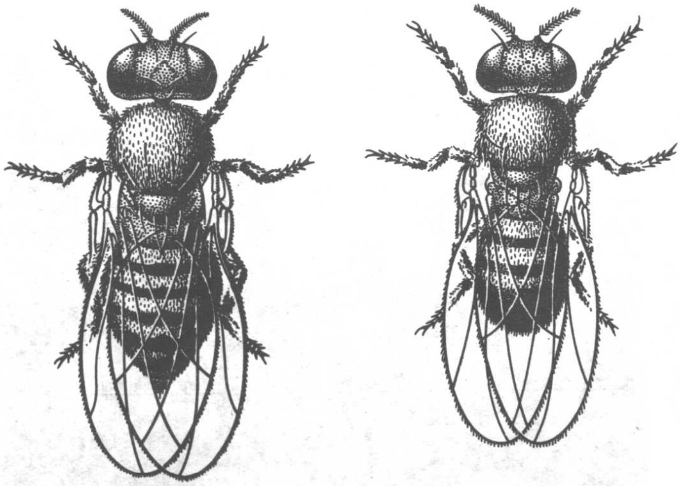

Fig. 1.3. Dorsal view of two flies, *Drosophila melanogaster*. (Left) Female; (right) male.

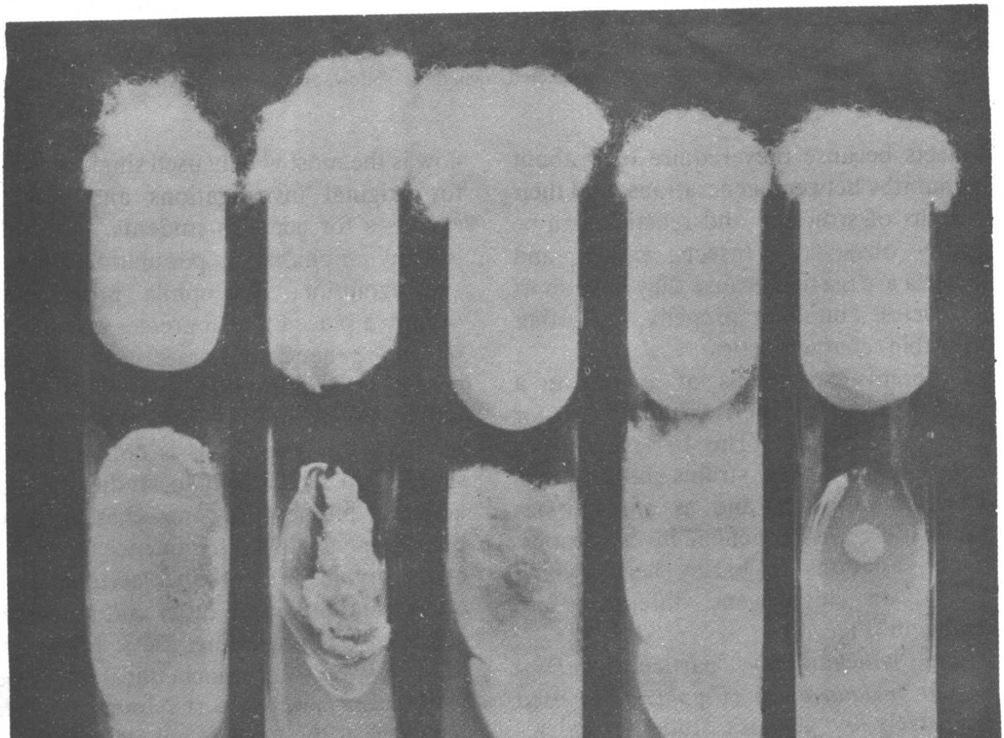

Fig. 1.4. *Neurospora crassa* colonial formations, left to right: crisp (orange color), colonial (buff), wild (orange), albino, button (gray).

Fig. 1.5. Twins which are much alike and probably identical, i.e., monozygotic. (Photograph by Lord from Monkmeyer Press)

Investigations Involving Twins

Identical or one-egg (monozygotic) (Fig. 1.5) twins develop from a common source (a single fertilized egg) and therefore both twins have identical genes. Differences between such a pair may be attributed primarily to environmental influences, and thus the relative importance of heredity and environment on the expression of various traits can be investigated. Fraternal (dizygotic) twins come from separate fertilized eggs and are no more closely related genetically than ordinary brothers and sisters (sibs). In twin studies designed to investigate the incidence of certain characteristics, fraternal twins may serve as a valuable control. On the average one in every 86 births is a twin birth. Thus two of 86 or about one in 43 babies born are twins. Despite the limitations of infrequent occurrence and the difficulty of distinguishing between monozygotic and dizygotic twins, studies of twins represent the most reliable method now available to researchers in human genetics.

Pedigree

The pedigree method consists of analyzing, for a particular trait, the results of matings already made. Diagrams or charts are usually constructed to symbolize individuals and illustrate relationships among them. From the data obtained, attempts are made to detect patterns of inheritance. This is the oldest method of genetic investigation and was used before the time of Christ. It is widely used in studies of human inheritance and is also applied to animal breeding.

Statistics

Sir Francis Galton (1822–1911; Fig. 1.6), human geneticist and biometrician of the last century, employed statistical tools extensively for human genetics studies.

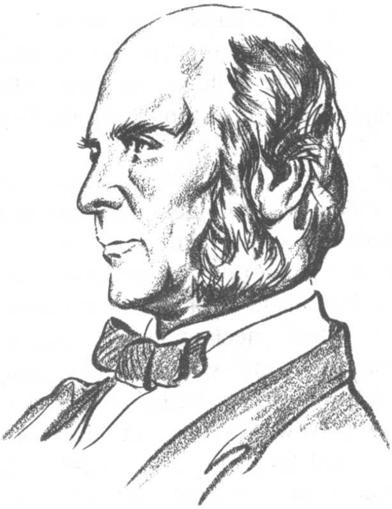

Fig. 1.6. Sir Francis Galton, English biometrician of the last century.

His work was critical and well designed, but unfortunately it was done before the foundation of Mendelian genetics was established. A large part of it, therefore, has required reinterpretation. Galton deserves much credit for pioneering in the use of mathematical tools that are now considered necessary for any research dealing with quantitative data. The use of statistical means by geneticists to control experiments and analyze results was revitalized by recent developments in population genetics. The outgrowth has been new applications of genetics to practical fields of plant and animal breeding.

Cytology

Cytological studies have been invaluable in establishing the physical basis of heredity and in discovering the nature and role of the nucleus, cytoplasm, and gene. Much interest has been centered around germ cells and their behavior. The geneticist who deals mainly with genes, which cannot be seen, is much more secure and confident of the validity of his results if he can point to physical, microscopically observable structures which are related to hereditary processes. The parallel between the mechanism postulated by the geneticist to account for his results and the observable cycle of the germ cells was a major factor in establishing the foundation of genetics.

At present, genetic theory is considerably ahead of cytological verification in all organisms and particularly in bacteria and viruses. Elaborate genetic evidence has been established for recombination and other genetic mechanisms in some groups of bacteria and viruses and cytological verification is now being obtained (Chapter 12). New methods and new tools must be devised to probe more deeply into the chemical and physical relations. Studies on these organisms have been especially fruitful in exploring the relations between genes and traits.

Biochemical and Biophysical Investigations of Genes

Special techniques have been applied to bacteria and other microorganisms with the objective of analyzing gene chemistry and gene action in organisms more simple than molds. *Escherichia coli* (the common colon bacillus), Pneumococcus (the pneumonia organism) and several other bacteria have been useful in biochemical genetics studies. Viruses, particularly bacteriophages (the type of virus that infects bacteria) are used for studies of the fine structure of the gene and gene action (Chapters 10 and 11). Modern tools such as electron microscopes and microspectrophotometers, and newly devised methods such as autoradiography (to be discussed in later chapters), have aided greatly in studies of the fine structure of the gene.

HISTORICAL SETTING

Modern geneticists often tend to ignore the "dead bones of the past" in their anxiety to probe more deeply into the problems of the present. Nevertheless some consideration of the way the science has developed is warranted. A brief summary of the historical background should enable us to visualize in better perspective the principles of genetics as we encounter them in subsequent chapters.

Practical accomplishments with some genetic overtones occurred in remote periods of history. Tablets of stone prepared by the Babylonians 6000 years ago have been interpreted to show pedigrees of several successive generations of horses, suggesting a conscious effort toward improvement. Other stone carvings of the same period illustrate artificial cross-pollination of the date palm as practiced by the early Babylonians. Many years before the Christian era, the early Chinese were improving varieties of rice. Maize was cultivated and improved in the Western Hemisphere before the Neolithic era. Methods of selection and hybridization were undoubtedly employed by early plant and animal breeders even though they were not aware of the principles of genetics.

Hippocrates, Aristotle, and other Greek philosophers made observations and engaged in speculations that suggested genetic principles. Their elements of truth, however, were vague and interspersed with error. Stories of unusual hybrids were initiated by the Greeks and repeated with additional imaginative flourishes by Pliny, Gesner, and other writers. These were perpetuated over a period of some 2000 years following the Greek period. The giraffe was supposed to be a hybrid between the camel and the leopard. The two-humped camel was thought to have resulted from a cross between a camel and a boar. When the camel mated with the sparrow an ostrich was imagined to appear. Plants also were considered capable of remarkable hybridizations. The acacia tree crossed with the palm was said to produce the banana tree. Fantastic explanations of the mechanism of reproduction and of sex determination were associated with these stories. Although many such tales persisted, little information existed before the seventeenth century that actually contributed to the science of genetics.

Sexual Reproduction in Animals

Much of the speculation of the ancients represented a sincere attempt to explain biological phenomena, but in the absence of facts, curious and more or less superstitious men resorted to imagination. A new era was introduced in the latter part of the seventeenth century by the development of the microscope and its effective use. Many years before the eggs and sperm of mammals were observed, however, William Harvey (1578–1657) had speculated that all animals arise from eggs and that the semen played a vitalizing role in the process. Only after the microscope made possible the discovery of the details of sexual reproduction, and the reproductive mechanism was described, however, could the genetic mechanism be discovered.

Three Dutch experimenters made major contributions toward furthering studies of reproduction in animals. First in chronological order was the Dutch physician, Regnier de Graaf (1641–1673), who observed that the progeny of mammals express characteristics of both the mother and the father. Therefore, he reasoned, both sexes must transmit agents of heredity. In search of some physical basis for this observation, he studied sections of ovaries prepared for examination. Fluid-filled spaces large enough to be seen without magnification, now called the Graafian follicles, were erroneously considered to be the eggs. In spite of this mistake, de Graaf was able to describe in general terms the process of ovulation and development of the embryo in the uterus of the mother. Even though mammalian eggs and sperm had not yet been actually observed, these beginnings in embryology prepared a foundation for the understanding of reproduction and heredity in animals. The mammalian egg was discovered by Von Baer in 1828.

The next significant contribution in the field, after that of de Graaf, came from the Dutch microscope maker Anton van Leeuwenhoek, who in 1677 observed sperm of several animals. He also observed the association of sperm with eggs in frogs and fish and considered the sperm to furnish the essential life-giving properties, while the egg merely provided the proper environment for nutrition and development of the embryo.

Two years later (1679) Jan Swammerdam, also using the microscope, studied the development of insects. He observed an unfolding process from stage to stage, or instar to instar, in the developmental sequence and visualized development as a simple enlargement from a minute but preformed animal to the adult. Later, after this idea had been applied too widely and supplemented by active imaginations, it was accepted as a general explanation of development and was known as the preformation theory. According to this theory, development consisted only of the enlargement of a preformed organism already present in the sperm or the egg. Some embryologists imagined that they saw little people, or homuculi (Fig. 1.7), in human sperm. Although the preformation theory as originally stated is now obsolete, it provided a mechanistic explanation of reproduction to replace the vague concepts of the earlier period.

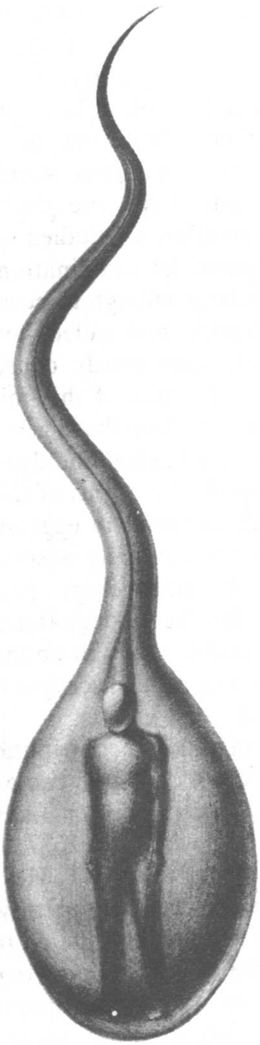

Fig. 1.7. Homunculus. Miniature human beings were imagined by some early preformationists to be present in sperm cells.

During the eighteenth and nineteenth centuries, much time, energy, and printed space were devoted to controversies between the ovists, who believed the egg contained the preformed animal, and the animalculists, who followed the view of Leeuwenhoek and insisted that the sperm carried the small but complete organism. Much writing space was also devoted to the more general argument between the preformationists and those (epigenesists) who believed that neither the sperm nor the egg contained a preformed embyro, but that they each contained undifferentiated living substance potentially capable of forming the complex organization of the animal body after fertilization.

The theory of epigenesis gained precedence in the latter part of the nineteenth century and has since proved to be essentially compatible with modern concepts of reproduction and heredity. The egg and sperm as now understood, however, do not represent entirely undifferentiated material. They have chromosomes that carry genes, which provide for a more subtle type of preformation. A modern evaluation of the merits of preformation and epigenesis would require a compromise. The individual organism is formed according to potentialities predetermined by the genes, but at the same time the individual represents more than a collection of genes. Profound interactions among the genes, their products, and the environment are involved in the development of the complex organism.

Sexual Reproduction and Hybridization in Plants

A basic understanding of sexual reproduction in plants also was achieved during the latter part of the seventeenth century. Plants are more simple in some respects and more easily controlled than animals. Thus they lend themselves more readily to experiments in hybridization. The discovery of sexual reproduction in plants, therefore, was a major factor in stimulating interest and experimentation in inheritance.

The first consistent studies which led to an understanding of the reproductive parts of plants were reported in 1682 by the English plant anatomist Nehemiah Grew. Twelve years later (1694) a German professor of medicine, Rudolph Camerarius, clearly described sexual reproduction in plants. This important contribution made possible the experimental approach to plant hybridization. Camerarius is also credited with the first artificially produced plant hybrid on record, from a cross between hemp and hop plants. In 1717 Thomas Fairchild, an Englishman, was reported by his contemporaries to have pollinated a carnation by a member of a related species (a pink). The hybrid, showing characteristics of both parents, was called Fairchild's Sweet William, and by some, "Fairchild's mule." No record of this hybridization was left by Fairchild himself, but there is good evidence that the reported results were actually obtained. Furthermore, the experiment was carefully designed, and the results were not accidental. Following this beginning, many artificial pollinations were performed between different related plants.

One of the most important reseachers in the eighteenth century was the German botanist Joseph Kölreuter (1733–1806). He found that hybrids between plant varieties might resemble one or the other parent or appear intermediate between them. Among his most valuable observations was the equality of contributions from the two parents in reciprocal crosses. That is, the same results were obtained by mating a male from variety A with a female from variety B as by mating a female from A with a male from B.

From one series of crosses between tall and dwarf varieties of tobacco, Kölreuter obtained results which foreshadowed the modern principle of quantitative inheritance. The first generation progeny were all intermediate between the two parents. In the second generation, variation was continuous from the size of the large parent to that of the small parent and a normal distribution was observed. The size of most of the second generation hybrids, however, fell between the extremes of the two parents. Kölreuter could not explain these results; in fact, not until the early part of the twentieth century was an adequate explanation obtained with the multiple gene hypothesis (Chapter 15).

Although general knowledge about sexual reproduction in plants and animals was accumulated in the eighteenth century, the important observation of actual fertilization was not made until the latter half of the nineteenth century. In 1855 Pringsheim first saw nuclear fusion in green algae (Vaucheria). Oscar Hertwig in 1875 observed the entrance of the sperm in the sea urchin egg. A single sperm was found to penetrate a single egg. This established a firm cytological basis for inheritance.

Pre-Medelian Explanations for the Origin of Variation

The Greek philosophers considered inherited characters of individuals to be acquired through direct contact with the environment. This idea, although not precisely stated until the eighteenth century, was widely accepted. The French scientist Jean Baptiste Lamarck (1744–1829; Fig. 1.8) formulated the common view of the eighteenth century biologists into a theory which bears his name and is known as the theory of inheritance of acquired characteristics. This theory emphasized use and disuse over long or short periods of time as the significant factors in determining the characteristics of the individual. The direct influence of the environment was considered to be impressed on the germinal material (eggs and sperm) and therefore transmitted in inheritance.

The bodily form and qualities of the individual were believed to be fashioned by the habits and manner of life of its ancestors. Fish living in deep, dark caves, for example, were blind, presumably because of disuse of their eyes. Flying birds, through use, acquired strong wings with well-developed muscles. Wading birds developed long legs, long necks, and long beaks. Frogs were considered to have obtained their webbed feet from stretching their toes in swimming. Among giraffes, the best neck stretchers could secure food from the tallest trees and this practice was set forth to account for giraffes with longer and longer necks.

Fig. 1.8. Jean Baptiste Lamarck, French biologist who formulated a view that was common among eighteenth century biologists into the theory of inheritance of acquired characteristics now called Lamarckism.

Climate, geographical conditions, and food requirements were believed to cause new organs to appear and old ones to disappear. Lamarck considered an animal's needs to determine its desires. The animal's desires, in turn, would determine the use or disuse of parts of the body, which would bring about modifications over long periods of time. According to the Lamarckian view these modifications would eventually find their way into the hereditary material. No such mechanism has ever been demonstrated experimentally, and present evidence concerning the nature of the germinal material and the developmental processes in plants and animals makes direct hereditary changes by environmental modification most unlikely.

An alternative explanation was provided by August Weismann (1834–1914), a German biologist, in the latter part of the nineteenth century. His theory was based on the early separation in the animal embryo between the germ plasm and somatoplasm. It emphasized the remarkable stability of the hereditary material. Little, if any, environmental influence could conceivably affect the genes, even though environmental modifications of external characters occurred. Reproduction in animals was accomplished not by body cells, that is, somatoplasm, but by the germ plasm, which was transmitted essentially unchanged from generation to generation. Although some details of the germ plasm theory have been modified, the fundamental premise is well established. Germ plasm is remarkably stable; however, it does occasionally undergo permanent but random change by mutation.

In plants there is no early separation between germ plasm and somatoplasm, and therefore Weismann's theoretical objection to the Lamarckian explanation would not hold. Each branch of a plant produces germinal or meristematic tissue each year. Nonhereditary changes may occur in seeds and appear in the plants, and hereditary changes occurring in the woody part of the plant may be transmitted to the progeny. There is a good theoretical basis, however, for rejecting the Lamarckian explanation for the origin of variation in plants as well as animals. Biochemical genetics has shown that a whole chain of chemical reactions must ordinarily occur between the determiner or gene and the trait it influences. The gene for example, may give rise to substance *A*, which produces substance *B*, which enters into the formation of substance *C*, and so on until the end product is formed. It is not likely that this process could go in reverse in such a way that the gene itself could be permanently changed.

Further evidence against the Lamarckian explanation for the origin of variation has come from the experimental work of Luria, Delbrück, and Lederberg on bacteria. When bacteria were irradiated first and later placed on selective media containing drugs usually lethal to the bacteria, a resistant organism would occasionally survive and produce progeny which were likewise resistant to the drug. It was shown that a mutation had occurred in the organism and that it was not the drug in the medium which was responsible for the hereditary alteration but the irradiation which preceded the selection. Control plates to which no poisons had been added also contained mutants that were resistant, indicating that the gene change was not brought about by the additive.

Fig. 1.9. Gregor Mendel, Austrian monk who became the father of genetics.

In the Western world the Lamarckian theory has been relegated to the historical realm, but in Russia it was revived a few years ago, under the leadership of Lysenko, to fit a political philosophy which developed in that country. A more detailed discussion of mutation and selection, which together provide a basis for explaining the origin and direction of variation in evolution, follows in later chapters.

Gregor Mendel

Because of his experiments with garden peas (*Pisum sativum*), Gregor Mendel (1822–1884; Fig. 1.9) is appropriately called the "father of genetics." His conclusions constitute the foundation of the modern science of genetics.

Throughout his life Mendel showed great interest in living things. His home community was a gardening and fruit-growing area, and he was raised on a small fruit farm. Mendel's father had great love for plants, especially fruit trees, and undoubtedly influenced his son as they worked together in the orchard. As Mendel grew older he became intensely interested in plant hybridization, and during his life he made crosses between varieties of many different plants, including the columbine, snapdragon, slipperwort, sedge, horse thistle, pumpkin, flax, stock, bean, pea, plum, pear, nasturtium, violet, maize, and hawkweed. Mendel also loved animals, both domesticated animals, which he cared for on the farm, and wild animals, which he observed with keen interest as he walked in the woods. For a time he kept a pet fox. He also maintained a colony of mice and made some attempts at breeding experiments with them.

Mendel received his early schooling in his home community and attended the preparatory school which was comparable to the present-day secondary school. Financial reverses at his home during the latter part of his preparatory schooling made it necessary for him to provide his own way and assist in supporting the family and maintaining the farm home. Because of overexertion and privation he suffered an illness which delayed completion of the course and impaired his health in later life. After his recovery he undertook a two-year course in philosophy.

On completion of the course he sought a livelihood which would be satisfying to him while not overtaxing his strength. Through the advice and assistance of his teacher, Professor Franz, he entered Altbrünn Monastery, an Augustinian religious community near Brünn, Austria, (now Brno, Czechoslovakia). On his twenty-fifth birthday (1847), he was ordained and became a monk. It was customary in the religious communities of that day for men to carry on creative work, either scientific or artistic, along with their religious duties. Mendel was thus encouraged to continue the work of his major interest on the hybridization of plants.

In 1849 a vacancy occurred in the nearby Zuaim preparatory school and Mendel obtained a temporary position as substitute teacher. He lacked the formal training required for certification as a regular teacher. After a successful year of teaching, he was granted a leave of absence from the monastery to study at the University of Vienna. At Vienna he took formal course work in science and mathematics that provided him sound background and aroused his interest in precise experimental work. When he did not succeed in passing the examinations required for teaching credentials, he returned to the monastery where his living was provided and he could pursue his experimental work.

Again in 1854 another vacancy occurred for a teacher, this time at the Brünn modern school, and Mendel was again employed as a substitute teacher. During the next fourteen years he continued as a temporary substitute teacher giving courses in physics and natural history. He had time for experiments, especially during summer vacations, and utilized a limited space in the monastery garden. These were the most pleasant and productive years of his life. The famous garden pea experiments were carried out in the monastery garden during the years 1856 to 1864. On the plaque now placed in the monastery garden is the inscription, "Praelat Gregor Mendel has made experiments for his law here," repeated in four languages, Czech, German, French, and English.

Mendel's students found him especially friendly and congenial. The following quotation[1] written by a student illustrates the human aspect of the man.

[1] *Life of Mendel*, by Hugo Iltis, W. W. Norton and Company, 1932, New York, pp. 92–93.